Research on drug abuse abstracts
1976/77

RESEARCH ON DRUG ABUSE ABSTRACTS 1976/77
RÉSUMÉS DE RECHERCHE SUR L'ABUS DES DROGUES 1976/77

Health and Welfare Canada
Santé et Bien-être social Canada

RESEARCH ON DRUG ABUSE
ABSTRACTS 1976/77

PROJECT OF THE NON-MEDICAL

USE OF DRUGS DIRECTORATE

RÉSUMÉS DE RECHERCHE SUR L'ABUS
DES DROGUES 1976/77

PROJET DE LA DIRECTION DE L'USAGE

NON MÉDICAL DES DROGUES

Published by authority of
the Honourable Marc Lalonde
Minister of National Health
and Welfare

Publication autorisée par
l'honorable Marc Lalonde
Ministre de la Santé nationale et du
Bien-être social

INTRODUCTION TO RODA ABSTRACTS

The Non-Medical Use of Drugs Directorate supports research directed toward providing information about all facets of drug abuse. The Directorate often receives requests from interested persons in the scientific community for detailed information concerning the research being supported. In response to these requests the Directorate makes available abstracts of all funded research projects.

The abstracts contained in this booklet are of a highly scientific and technical nature and are therefore published in the language of the authors. No attempt has been made by the Directorate to edit or evaluate this material and the abstracts are reproduced directly from the form that was sent to the researchers. All abstracts received in Ottawa by the deadline date are presented in the booklet. It is regrettable that some researchers were unable to submit their abstracts in time for inclusion. The appendix contains the names of all researchers we are funding.

For the convenience of readers, the abstracts in this book have been divided into five categories. These categories are evaluation, biomedical, behavioural, social science and multidisciplinary. Within each category, projects are presented according to the alphabetical order of the surname of the principal investigators.

It is with pleasure that the Non-Medical Use of Drugs Directorate presents to you this booklet of abstracts.

INTRODUCTION AUX RÉSUMÉS DE PROJETS DU PROGRAMME DE RECHERCHE SUR L'ABUS DES DROGUES

La Direction de l'usage non médical des drogues subventionne des recherches visant à fournir des renseignements sur tous les aspects de l'abus des drogues. La Direction reçoit souvent des demandes de renseignements de personnes intéressées, du domaine scientifique, sur la recherche subventionnée. Pour répondre à ces demandes la Direction présente les résumés de projets de recherche subventionnés.

Les résumés présentés dans cette brochure sont de nature scientifique et technique et paraissent donc dans la langue de l'auteur. La Direction n'a ni révisé ni évalué ces ouvrages et a reproduit les textes directement du formulaire envoyé aux chercheurs. Tous les résumés reçus à Ottawa avant la date limite sont présentés dans cette publication. Il est regrettable que certains aient été reçus trop tard pour y être insérés. Les noms de tous les boursiers figurent en appendice.

Pour faciliter la consultation, les résumés sont divisés en cinq catégories: évaluation, recherche biomédicale, recherche sur le comportement, sciences sociales et recherche multidisciplinaire. Au sein de chaque catégorie, les projets sont classés selon l'ordre alphabétique des noms des principaux chercheurs.

C'est avec plaisir que la Direction de l'usage non médical des drogues vous présente cette brochure de résumés.

TABLE OF CONTENTS
TABLE DES MATIÈRES

EVALUATION
ÉVALUATION

MULTI-DISCIPLINARY
MULTI-DISCIPLINAIRE

SOCIAL SCIENCE
SCIENCES SOCIALES

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DÉPARTEMENT
J.Allan Best, Ph.D.	Psychology

INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE
University of British Columbia, Vancouver, British Columbia. V6T 1W5

PROJECT TITLE TITRE DU PROJET
SMOKING WITHDRAWAL PROCEDURES TAILORED TO INDIVIDUAL REASONS FOR SMOKING

YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1974 - 1978	$92,001.52	228-2755

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION
[ ] BIOMEDICAL BIOMEDICALE
[X] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

SMOKING WITHDRAWAL PROCEDURES TAILORED TO INDIVIDUAL REASONS FOR SMOKING

The primary objectives of the project are (a) to provide an empirical basis for tailoring smoking cessation procedures to individual smoking patterns and (b) to develop effective, self-managed smoking cessation procedures amenable to public health and preventive medical utilization. Cessation is conceptualized as involving two sequential phases with distinct methodologies: an initial change stage for which aversive oversmoking procedures have been shown effective, and a subsequent maintenance of change stage. Maintenance has typically not been considered in previous research and relapse is generally extensive.

Maintenance is hypothesized to require the acquisition of nonsmoking behaviours. Two types of nonsmoking behaviour are identified: (a) responses which are functionally equivalent to smoking in that they have similar instrumental value and (b) more general self-control responses used to cope with the over-learned situational components of the smoking habit.

The treatment programme currently employed requires five weekly sessions and includes both behavioural self-management training and aversive oversmoking procedures. Results from nine, controlled outcome studies to date may be summarized as follows. The show (a) high levels of short-term (80% abstinence) and long-term (50% abstinence) success, (b) the importance of including both cognitive and behavioural modification techniques, (c) a tendency to superior results for clients seen in smaller groups, (d) the importance of written instructions in improving compliance with the treatment regimen, (e) the detrimental effect of fostering undue reliance on the clinic through between-session supportive telephone calls, and (f) the particular potency of an intensive version of the programme, through the addition of sensory deprivation procedures (80% abstinence at 6 month follow-up). Preliminary data also support the effectiveness of a staff training programme. An adaptation of the programme for commercial television use is currently being evaluated.

Proposed future outcome studies will evaluate long-term effectiveness of two variations on the treatment programme developed previously. The first variation will utilize controlled smoking rather than complete abstinence as the goal for treatment. The second variation will use self- and large-group-administration alternatives to the small group format used to date. The relative efficacy of alternative staff training models will be evaluated. A comprehensive programme evaluation study is proposed to monitor the programme's implementation in various health services.

A separate line of research examines methodological and conceptual issues in the assessment of individual smoking patterns. A situational model of smoking behaviour is being developed factor analytically. It will provide a basis for a topology of smokers to be used in developing guidelines for individualizing the cessation programme.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER - NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT - DÉPARTEMENT
R.M. Gilbert	Research

INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE
Addiction Research Foundation, 33 Russell Street, Toronto, M5S 2S1

PROJECT TITLE TITRE DU PROJET
Temporal and volitional factors in the development and assessment of physical dependence on ethanol in rats.

YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1975-76, 1976-77 (part of each)	$16,804 + $4,234.92 = $21,038.92	(416) 595-6169

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMEDICALE [X] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Description of Project

The primary concern was with the role of degree of dose division in the development of physical dependence on ethanol: more specifically, does the severity of dependence resulting from chronic administration of a given daily dose of ethanol vary with the frequency of division of the dose? For example, are withdrawal symptoms more severe if 8 g/kg is given in one daily dose or in four 2 g/kg portions every 6 hours?

The secondary concern was with the role of 'voluntary' consumption of ethanol. Does the severity of physical dependence vary according to whether the ethanol is drunk by the animal or forcibly administered, and to whether withdrawal is precipitated by removing ethanol or by providing a more palatable fluid?

Ethanol drinking sufficient to cause physical dependence was induced by spaced feeding of small portions of the food ration (schedule induction). Ethanol was otherwise administered by gastric tube.

Recorded signs of withdrawal included general hyperactivity, spontaneous tremors, and spontaneous and sound-induced seizures.

The project was funded by NMUD in 2 parts. Initial funding of $16,804 supported the project from October 1975-July 1976. A terminal award of $4,234.92 provided further support until November 1976.

2. Key findings

Three experiments were completed. Two involved gastric intubation of a given daily dose of alcohol by different degrees of division. In both experiments, rats having the least divided alcohol dose were more likely to exhibit audiogenic seizures during alcohol withdrawal. The greater susceptibility to seizures was tentatively attributed to the manifest debility of the rats receiving the whole of their daily dose within a brief period. The debility resulted from a suppression of eating by the alcohol administration regimen.

The third experiment compared alcohol consumption and withdrawal effects when the daily food ration of 360 pellets was presented in one 6-hour session or in six, equally spaced 1-hour sessions, pellets being delivered at 1-min intervals. Rats having a 1-hour session every four hours showed slightly more withdrawal stress than rats having a 6-hour session every 24 hours. There were two different kinds of indication of possible loss of control over alcohol drinking by the inducing schedule: (i) Rats experiencing six sessions a day did not drink water excessively when it replaced the alcohol solution, suggesting that the excessive drinking of alcohol was being maintained by some property of the alcohol. (ii) Rats experiencing one session a day drank half their total alcohol intake between

sessions, but almost none of their water, indicating that the inducing schedule was able to control the temporal distribution of water but not alcohol consumption.

3. Significance of project

The results of the first two experiments demonstrate that the most-used method of assessing physical dependence on alcohol is unsuitable as a method of investigating the relation between dose division and the severity of dependence. The results of the third experiment pose questions about the validity of the schedule-induction model of human alcohol abuse.

4. Relevance of project

The question of the role of dose division (or drinking pattern) in the development of alcohol dependence remains relevant. If animal studies are able to define the basic parameters of the relationship, it may be possible to gain some useful indicators of the involvement of physical dependence in individual cases of alcohol abuse.

The utility of the schedule-induction model of human alcohol abuse is not ruled out by the results of the third experiment. It appears, however, that the chief relevance of the model may be to the development rather than to the maintenance of abuse.

5. Future directions

The results of the first two experiments suggest that more sensitive indicators of physical dependence on alcohol are required. The NMUD-funded work has stimulated ARF-supported work to establish such indicators. Further work may be conducted on the role of spaced feeding in the development of excessive alcohol drinking in rats.

May 16, 1977

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Robert W. Hetherington	Psychiatry
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of Saskatchewan, Saskatoon, Sask. S7N 0W0	
PROJECT TITLE – TITRE DU PROJET	
Teenage Alcohol Consumption: An Epidemiological Baseline in Saskatchewan Schools	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES / TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
Oct. 1976 - August 1977	$29,347.00 / 343-2041

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [ ] BIOMEDICAL BIOMÉDICALE [x] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

To date there has been no definitive study conducted in Saskatchewan which would explore the extent of alcohol use by the teenage population. Clinical and experiential evidence locally, as well as evidence from other areas of Canada, indicate that drinking problems are more commonly found among younger and younger age populations over time.

This study was prompted by evidence of more teenagers drinking, of higher consumption rates for teenagers that do drink, and teenagers drinking at earlier ages. It is an epidemiological survey of drinking behavior among Saskatchewan students in grades 6 - 12. Results from the study are not yet available.

Data has been collected in Saskatoon and two rural school districts. A random sample of 500 students was selected in each of the three areas. In each region, one half of the students were interviewed and the other half were administered a questionnaire.

Information was collected on topics such as knowledge about alcohol and its effects, sources of information about alcohol, attitudes towards drinking, perceptions of peer group and family drinking, personal consumption and family, religious and socio-economic background.

The major interest is in distributions of the sample across socio-demographic and other variables. We will attempt to relate the three outcome measures -- level of consumption, attitudes and knowledge -- statistically to independent variables (e.g., rural-urban place of residence, ethnicity, grade-level, etc.). There is also great interest in statistical relationships among the outcome measures themselves, since "attitudes and knowledge" may be affected by subsequent programs.

Data from this survey are intended to serve as baseline information to aid in determining the need for educational programs designed to foster healthy attitudes toward alcohol and to modify drinking patterns. The Alcoholism Commission of Saskatchewan is prepared to provide consultative and/or educational services as requested and deemed appropriate by educational authorities at system or individual school levels. The Applied Research Unit is prepared to evaluate any resulting educational programs using a cohort approach over time.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
R. O. Pihl R.O. Pihl	Psychology

INSTITUTION AND ADDRESS - ÉTABLISSEMENT ET ADRESSE
1205 McGregor Avenue, Montreal, Quebec H3A 1B1

PROJECT TITLE TITRE DU PROJET
Extrapharmacological Factors in Drug Intoxication

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
		392-4702

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION
[ ] BIOMEDICAL BIOMEDICALE
[x] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Thirty-one papers and conference presentations have resulted from NMUD funded research. Findings can be summarized under three headings. First, The Specification of Intoxication; studies have been completed that demonstrate that marijuana intoxication is a verbally definable experience which varies with degree of experience with the drug, that the experience differs geographically, that expectancy is important in producing the effect, even among very chronic users on the Island of Jamaica, and that marijuana intoxication can be detected by non-intoxicated observers. Second, The Manipulation of Marijuana and Alcohol Intoxicated States; a series of completed experiments show that the social situation affects degree of marijuana intoxication, that women respond socially in a different manner to this drug than men, that expectation is important in producing the acute response, that time perception distortions vary depending on how the question is asked, that the high can be disrupted, that the high seems independent of changes in heart rate, that motivation is affected by the drug, and with alcohol, that the ability to compensate for alcohol-produced decrements exists. Third, The Role of Individual Factors in Intoxication; completed work illustrates the interaction between the individual and the drug in producing an effect. It is argued that to truly understand abuse, we must not only be concerned with what drugs do to people, but also with what people can do to drugs.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. Z. Amit	Psychology-Center for Research on Drug / Dependence

INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE
Concordia University, 1455 de Maisonneuve Blvd. W., Montreal, Que. H3G 1M8

PROJECT TITLE TITRE DU PROJET
Development of a Treatment Model for Alcholics.

YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TELEPHONE
1976	$ 14,500	879-8021

FIELD OF RESEARCH SUJET DE LA RECHERCHE	EVALUATION ÉVALUATION	BIOMEDICAL BIOMEDICALE	BEHAVIORAL COMPORTEMENT	SOCIAL SCIENCE SCIENCES SOCIALES	MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE
	[ ]	[X]	[X]	[ ]	[ ]

This project attempted to investigate the effects on alcohol intake of brain norepinephrine depletion by inhibition of the enzyme dopamine-beta-hydroxylase. The rationale underlying this project has been that in order to produce a relatively stable reduction and control over alcohol intake, one must attempt to separate the act of drinking alcohol from the reinforcement which the drinking produces. It has been our contention that this is the critical factor maintaining alcohol preference, both in animals and humans. There is considerable evidence pointing at the involvement of norepinephrine in the regulation of ethanol intake by modulating ethanol's positive reinforcing properties. In our own laboratory, we have found that injections of FLA-63 and FLA-57 (both known to be potent inhibitors of dopamine-beta-hydroxylase) effectively reduced ethanol intake in ethanol-preferring rats. However, when the injection regimen had been terminated, ethanol intake quickly returned to pre-injection baseline levels. From the point of view of learning theory, this is not surprising, since in order to suppress an undesirable response for a long period of time, one must attempt to extinguish it. In order for this to occur, the organism must perform the response in the absence of reinforcement. However, in the experiments described above, the animals ceased to perform the response as a result of the FLA injections, and thus no extinction was expected. In the present project, we attempted to extinguish the drinking response by pairing forced ethanol drinking with FLA-57 injections. In the post-injection period, we reinstated the animals on free-choice between ethanol and tap water. We have found that pairing forced drinking of ethanol with FLA injections produced a long-lasting and marked reduction in ethanol preference in the post-injection period. We would like to emphasize that this reluctance to drink ethanol was observed in animals which preferred ethanol for at least 40 days prior to the beginning of the injection period.

To the best of our knowledge this is the first manipulation of ethanol-preferring animals which resulted in a long-term reluctance to ingest ethanol in the post-experimental period. We feel that these findings comprise a considerable contribution to the understanding of the mechanisms underlying alcohol preference and dependence by focussing attention on the mechanisms mediating the euphoric properties of ethanol and which tend to reinforce the continuation of ethanol-oriented behaviour. These findings also contain implications for the development of new treatment procedures for alcoholics. By separating the act of drinking from its reinforcing consequences it is conceivable that we could obtain an alcoholic who would "voluntarily" abstain or at least reduce his alcohol intake to manageable levels. This period of reduced ethanol intake would permit other therapeutic interventions such as environmental restructuring and the training of new coping styles to be implemented.

Dr. Z. Amit.

Publications

1 Amit, Z., Levitan, D.E., & Lindros, K.O. Suppression of ethanol intake following administration of dopamine-beta-hydroxylase inhibitors in rats. Archives Internationales de Pharmacodynamie et de Thérapie, 223, 114-119, 1976.

2 Amit, Z., Brown, Z.W., Levitan, D.E., & Ogren, S.O. Noradrenergic mediation of the positive reinforcing properties of ethanol: I. Suppression of ethanol consumption in laboratory rats following dopamine-beta-hydroxylase inhibition. Submitted for publication.

3 Brown, Z.W., Amit, Z., Levitan, D.E., Ogren, S.O., & Sutherland, E.A. Noradrenergic mediation of the positive reinforcing properties of ethanol: II. Extinction of ethanol-drinking behaviour in laboratory rats by inhibition of dopamine-beta-hydroxylase. Implications for treatment procedures in human alcoholics. Submitted for publication.

4 Amit, Z., Brown, Z.W., & Sutherland, E.A. Extinction of ethanol preference by dopamine-beta-hydroxylase inhibition. Implications for a treatment model for alcoholics. To be presented at the National Council on Alcoholism Meeting, San Diego, 1977.

5 Amit, Z., Brown, Z.W., & Rockman, G. Possible involvement of acetaldehyde, norepinephrine and their TIQ derivates in the regulation of ethanol self-administration. To be presented at the Milton M. Gross Memorial Symposium on Alcoholism, Chicago, 1977.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER - NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DÉPARTEMENT
Dr. P.K. Basrur	Biomedical Sciences

INSTITUTION AND ADDRESS - ÉTABLISSEMENT ET ADRESSE
University of Guelpn, Guelpn, Ontario. N1G 2W2

PROJECT TITLE TITRE DU PROJET
Studies Related to the Test Systems and Biological Activities of Cigarette Smoke

YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNEES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1975 - 1978	$350,000.00	824-4120

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION
[X] BIOMEDICAL BIOMÉDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

COMPARISON OF MUTAGENICITY TEST DATA ON CANADIAN COMMERCIAL CIGARETTES WITH THEIR TAR AND NICOTINE LEVELS

Studies were undertaken to test whether the tar and nicotine levels of cigarettes reflect (or influence) their mutagenicity.

These studies were conducted on Salmonella typhimurium using Ames' method, using 2 cigarettes each of high, low and medium tar-nicotine. The tests were carried out with fresh whole smoke and smoke condensate.

The results showed that the lowest mutagenicity was in the cigarette with the lowest tar-nicotine values. However, of the 2 high tar-nicotine cigarettes only one was high in mutagenicity while the other was intermediate.

The data indicate that the cigarette with the lowest tar-nicotine value can be picked up as the lowest by the mutagenicity test. Since the LHC programme relies on the ability to recognize a biologically less harmful cigarette, the mutagenicity adds to the reliability of the least harmful cigarette picked up by tar-nicotine criteria. The data also shows that the highest tar content doesn't invariably indicate highest biological activity.

MUTAGENICITY TESTS ON THE 16 CIGARETTES OF THE PHASE II SERIES

Experiments were conducted to test the mutagenicity of a variety of tobaccos known to have varying alkaloid levels.

The test system used was Salmonella typhimurium exposed to the method described by Ames. It was noted that the least mutagenic cigarette was Delhi 34 and the most mutagenic cigarette was Vince. As compared to Minitor 'C' 9 of these cigarettes were significantly lower in mutagenicity whereas 7 were not. Increased nicotine content didn't increase mutagenicity.

The purpose of the test was to determine whether or not increasing the level of alkaloids in tobacco would increase its biological ill effects, since the trend (in some U.S. experiments) has been to increase the nicotine levels in tobacco in an attempt to increase the acceptability of cigarettes to consumer. Since the measures to reduce the tar content also reduce the nicotine content, it would be advantageous to select high nicotine - low tar tobacco for experiments related to developing a cigarette that is less hazardous and acceptable to consumer.

SHORT TERM MOUSE SKIN RESPONSE TEST ON 16 CIGARETTES OF THE PHASE I SERIES

Experiments were undertaken to compare the short term bioassay results of Canadian experimental cigarettes with their tar and nicotine levels and the levels of other chemical constitutents.

The criteria used were the sebaceous gland suppression (SGS) response, and epidermal hyperplasia (EH) response using ten animals per group, two slides per animal and 10 fields per slide as described in report to NHW in 1975.

It was noted that the most active cigarettes on the basis of SGS response to 10% condensate were cigarettes 205 and 756 (flue cured, whole plant leaf blend without high efficiency filter and 50% cytrel) and the least active were 514 and 454 (flue cured, whole plant stem blend with and without homogenization). EH response test picked up one of the lease active cigarettes (454) while the other (514) was among those showing higher response. The tests also showed that the EH response is not always concentration dependent.

Mouse skin response test is being used as a screening test in various places. Recently, Boch had shown a correlation between SGS and nicotine content of tobacco. The present study shows that the most active cigarette SGS criteria is the highest in tar-nicotine content and the least active is the lowest in nicotine content but of medium tar content. However, the cigarette with lowest tar content and absent in nicotine is among the third lowest in SGS response. The parameters tested are indicative of biological response to different constituents in cigarette smoke - not only to total tar or nicotine contents. The results of chemical assay on these cigarettes will be helpful in the interpretation of the bioassay data.

SHORT TERM INHALATION TESTS ON CANADIAN CIGARETTE, MONITOR 'C'

Experiments were undertaken to study the effect of smoke from different amounts of Monitor 'C' on the hamster respiratory tract.

The animals used were 20 hamsters each in control, sham smoked and smoke exposed groups, the latter receiving 4 and 8 cigarettes for 3 weeks.

Histological examination of the respiratory mucosa, lung parenchyma and nasal mucosa at the termination of the experiment showed that hamsters exposed to 8 cigarettes for 3 weeks had higher incidence of rhinitis, focal squamous metaplasia of the mucosal linings of the air ways, desquamation of ciliated cells and aggregation of alveolar macrophages than that in the other 3 groups. Those exposed to 4 cigarettes showed these alterations at a less severe degree but greater than those of sham smoked and control.

The results of these experiments suggest that short term exposure to cigarette smoke may be useful in assessing the biological response to the cigarette inhaled. However, the method of quantitating these changes are subject to criticism as most of the current methods in histopathologic studies. This aspect of tobacco research is in experimental stage in most countries including U.S. and U.K. at present.

THE FEASIBILITY OF USING ARYL HYDROCARBON HYDROXYLASE (AHH) INDUCTION AS A MEANS OF RATING CIGARETTES

Experiments were undertaken to test whether the AHH induction parameter can be used as a means of selecting hamsters for inhalation studies or as an end point in bioassays on cigarettes.

A pilot test was first undertaken to test what tissues show measurable induction of AHH and later the test was extended to determine what level of induction is caused by cigarettes which have shown high and low response in other biological tests.

The animals used were hamsters exposed to smoke from 205 for a week (20 cigarettes) and the tissues examined were liver, lung, skin and kidney (Part I). The cigarettes tested included Monitor 'C', 205, 053, and 848.

It was noted that the highest level of induction is in lungs in hamsters exposed to 205. The test also showed that Monitor 'C' and 053 which are similar in tar content and skin response test but differ in biological activity (mutagenicity test) are similar on AHH induction criteria; 848 which is low in tar-nicotine level and mutagenicity from 205 is higher on AHH criteria than 205.

The tests do not seem to add much to the strength of results with other bioassays. Since the method also is involved and expensive, the value of the test is bioassays appears to be limited.

INFLUENCE OF VITAMIN A DEFICIENCY ON THE HAMSTERS' RESPONSE TO SMOKE INHALATION

Experiments were conducted to test whether hypovitaminosis A condition can shorten the time required for the prenepolastic alterations in hamsters. The animals used in the experiment were 20 hamsters each in control, sham smoked, smoke exposed with and without prior treatment with vitamin A deficient diet.

The animals were histologically examined after their plasma was collected for Vitamin A determination.

The results showed that hamsters exposed to smoke show lower levels of Vitamin A in their liver and kidney but not in plasma. Incidences of squamous metaplasia and alveolar bronchiolization were greater in smoke-exposed hamsters which were Vitamin A deficient than in the other groups.

The long time required for the induction of tumors in the lungs in animals exposed to cigarette smoke inhalation and the low incidence of these tumors have been a great disadvantage which discouraged people from using inhalation tests in bioassays. However, inhalation tests are required to gather information on the biological insult a cigarette is capable of producing not only to the lungs but to a variety of other organs. If the duration can be reduced with pretreatment or with the manipulation of nutritional status, this important test system can be used without encountering enormous expense of time and money. (These studies are in progress).

MUTAGENICITY TESTS ON URINE SAMPLES OF HAMSTERS EXPOSED TO CIGARETTE SMOKE

An experiment was undertaken to test whether or not the urine samples of hamsters exposed to cigarette smoke are mutagenic. The test system involved Salmonella typhymurium strains TA 98 and TA 100 and the cigarettes used were 205 (flue-cured, whole plant leaf blend; high TPM, tar and nicotine: 26.7; 22.1 and 1.77 respectively). The animals were exposed to smoke for one day, four weeks, the latter with and without recovery period.

It was noted that the urine samples from hamsters exposed to smoke from cigarette 205 were not mutagenic irrespective of the duration of smoke inhalation.

A variety of carcinogens have been shown to be mutagenic in the Salmonella test systems and some of the chemicals which are not carcinogenic or mutagenic as such, become converted to mutagens and carcinogens in the animals and these metabolites are excreted in the urine. If the urine samples of animals exposed to smoke inhalation were mutagenic, the extension of this project would have been to test a batch of cigarettes to see if they can be ranked according to their mutagenic potential. This would have been another handle to assessing the biological activity of the cigarettes in the LHC program.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Bernard BELLEAU	Chemistry, Otto Maass Chemistry Bldg.

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
McGill University, 801 Sherbrooke Street West, Montreal, Quebec, H3A 2K6

PROJECT TITLE TITRE DU PROJET
In vivo N-dealkylation of Opiates in Relation to Agonist-Antagonist Actions

YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
(2) two years 1974-76	$32,841.00	392-5926

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMÉDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Brief description of research project. Strong analgesics devoid of narcotic properties are awaited anxiously in medicine. Analysis of structure-activity relationships among narcotic antagonists led to the working hypothesis that pharmacological cleanliness may depend in part on the susceptibility of morphinans and their analogs to microsomal N-dealkylation in the liver and brain tissue. Recently, active N-demethylation of morphine in brain was demonstrated. Since N-dealkylated opiates and their antagonists generally behave as narcotics, the question arose as to whether the pharmacological cleanliness of Oxilorphan and Butorphanol (a potent non-narcotic analgesic) was related in any way to their susceptibility or resistance to in vivo N-dealkylation. This knowledge would be of great value since it would help in the design of improved non-narcotic analgesics displaying strong resistance toward N-dealkylation. Suitable enzymatic assay had to be developped at first and the longer range goal was to design selective and potent inhibitors of N-dealkylase.

2. Summary of major developments. Published methodology for the assay of opiate N-demethylase activity in liver and brain tissue was found to be totally inadequate for routine studies of structure-activity relationships. We therefore attempted the development of a new accurate routine assay for aldehydes. The new assay based on Purpald is of such a nature as to allow for several precise determinations of the semicarbazide complexes of aldehydes. However, high blanks are obtained with liver microsomes. This can be improved by prior Sephadex filtration which removes the pyridine nucleotide co-factor. The blanks are still somewhat high but purification of N-dealkylase indicates that the assay might be suitable for routine use. Nevertheless, evidence has been obtained that Oxilorphan and Butorphanol are not significantly N-dealkylated. Instead, Butorphanol is hydroxylated in the side-chain and the new compound shown by others to possess a pharmacological profile similar to Cyclazocine. We may therefore have the basis of a partial explanation for the pharmacological cleanliness of Butorphanol.

3. Importance of project. Narcotics abuse is a major social problem. The development of pure, long-lasting antagonists would help in the rehabilitation of addicts whereas the development of synthetic non-narcotic analgesics would curb our dependence on opium as a source of medicinals that lead to abuse. Drug developpers need basic information on the physiological parameters responsible for narcotic side effects so as to design structures retaining only the desired properties of opiates and their antagonists. Since the N-dealkylated analogs of opiates or their antagonists uniformly exhibit narcotic properties, basic information on the structural parameters affecting N-dealkylation or inhibition of N-dealkylation in vivo is of paramount importance so as to design drug structures refractory or inhibitory to this degradative reaction. A first step in that direction appears to be Butorphanol.

4. Summary of discoveries likely to reduce problems associated with the non-medical use of drugs. The as yet fragmentary information obtained as regards the resistance of Butorphanol and Oxilorphan toward N-dealkylation in vivo is most useful to drug developpers engaged in the search for medically acceptable substitutes for the opiates. Structural modifications of Butorphanol have already been accomplished keeping in mind that resistance to in vivo N-dealkylation may be an important parameter contributing to the pharmacological cleanliness of the desired substitutes. Our fragmentary results and working hypotheses have provided an additional stimulus for the development of safe opium substitutes. This goal seems to have been attained and one can foresee a lessening of our dependence on opium as a source of drugs. There is little doubt that once the medicinal chemist becomes aware of the in vivo parameters that are responsible for the side effects of narcotics, he will be able to design structures retaining only the desirable properties of opiates. The elimination of opium from the arsenal of medicinal agents will allow a much better control of the non-medical use of narcotics.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR
G.D. Bellward, F.S. Abbott and J.E. Axelson

DEPARTMENT - DEPARTEMENT
Faculty of Pharmaceutical Sciences

INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE
University of British Columbia, 2075 Wesbrook Mall, Vancouver, B.C. V6T 1W5

PROJECT TITLE TITRE DU PROJET
Pharmacokinetics and Metabolism of Methadone

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1974-1977	75,820	604-228-4103

FIELD OF RESEARCH SUJET DE LA RECHERCHE

[ ] EVALUATION ÉVALUATION	[X] BIOMEDICAL BIOMEDICALE	[ ] BEHAVIORAL COMPORTEMENT	[ ] SOCIAL SCIENCE SCIENCES SOCIALES	[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Project A

Twelve male patients stabilized on methadone for many months or years were studied. A comparison was made of the plasma levels and renal clearance of this drug between those patients on "high" doses (80-110 mg/day) vs those on "low" doses (15-40 mg/day). A general trend to higher renal clearance was seen in the "high" dose group. However, on more detailed examination, a direct correlation was seen when the patients were categorized according to urinary pH. At low pH's, a nearly 3-fold increase in renal clearance was noted. This was reflected by a decreased major metabolite to methadone ratio. No evidence for a difference in rate of metabolism between the two groups was seen, nor were there differences in hepatic function. It was concluded that urine pH was a major factor in renal clearance of methadone in these patients.

Project B

Methadone HCl added to the drinking water of adult female Wistar rats for 4 weeks produced an increase in the aryl hydrocarbon hydroxylase activity of the hepatic microsomal fraction to 222% of control levels. No change was seen in epoxide hydrase activity. In contrast, when male rats were treated similarly, there was an increase in epoxide hydrase activity to 212% of controls with no change in aryl hydrocarbon hydroxylase activity. No such changes were observed using the subcutaneous route of administration or chronic low dose intraperitoneal injections. There were no differences in hepatic cytochrome P-450 or protein concentration in treated animals as compared to their respective control groups. Control studies were carried out with quinine sulfate in the drinking water to decrease water intake to the level of the methadone-treated group. No elevation in either enzyme activity occurred in this control group. Similarly, paired feeding studies showed the elevation of enzyme activity to be due to the methadone, not food deprivation. The effects of concurrent therapy of methadone with phenobarbital sodium, or 3-methylcholanthrene were compared.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Birmingham, M.K. and Bartova, A.	Psychiatry, McGill University

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
Allan Memorial Institute, 1033 Pine Avenue West, Montreal, Quebec H3A 1A1

PROJECT TITLE — TITRE DU PROJET
Effects of Δ^9-THC on Mitochondrial Respiration

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
April 1, 1976 to June 30, 1976	$ 5,772.50	342-1251, ext.1614 - 1617

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [XX] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Brief Description

The research program in this continued investigation has been designed to examine the kinetics of the inhibition by Δ^9-THC of the particulate-bound enzyme systems of mitochondrial inner membrane - NADH-oxidase and NADH-cytochrome-c-reductase, and the site and mode of action of the drug in the electron transfer chain.

2. Statement of Problem

We have observed that Δ^9-THC is a highly effective inhibitor of brain and heart NADH-oxidase activity in vitro, and after an acute administration in vivo, of the NADH-oxidase activity of rat brain but not rat heart mitochondria. There were indications that the NADH-cytochrome-c-reductase reaction was the site of the inhibitory effect of Δ^9-THC. For the study on the site of Δ^9-THC action in the respiratory enzyme chain, the specific intracellular location of the inhibition and for the precise nature of this inhibition well characterized cell fractions from rat and bovine hearts were employed.

3. Key Findings

The site of inhibition by Δ^9-THC in the electron transfer chain was investigated between NADH and flavoprotein, between flavoprotein and CoQ and between cytochrome b and c_1. The inhibition by Δ^9-THC appeared to be at or near the amytal-sensitive site of the electron transfer chain; i.e. between flavoprotein above the cytochrome c site. This inhibition exceeded the effect of deoxycorticosterone, a known inhibitor of this enzyme system by three to five times and of amytal by two to three orders of magnitude. Kinetic studies using Lineweaver and Burk's graphical method characterized a competitive type of inhibition of rat heart NADH-cytochrome-c-reductase defined by a statistically not significant change in V_{max} from 1.67×10^{-5} M/min/mg to 1.2×10^{-6} M/min/mg and by an increase in K_m from 4.5×10^{-5} M to 2.12×10^{-4} M.

4. Significance

Previous studies from this laboratory have focused on the effects of Δ^9-THC on the brain and heart enzyme systems, NADH-oxidase and NADH-cytochrome-c-reductase. The present study contributed to the elucidation of the basic mechanism of action of this drug.

Publication

Bartova, A.; Birmingham, M.K.
Effect of Δ^9-Tetrahydrocannabinol on Mitochondrial NADH-oxidase Activity.
J. Biol. Chem. 251, p. 5002-5006, 1976

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER / NOM ET SIGNATURE DU CHERCHEUR	Ian R. Brown Ian R Brown
DEPARTMENT – DÉPARTEMENT	Zoology
INSTITUTION AND ADDRESS / ÉTABLISSEMENT ET ADRESSE	University of Toronto, Toronto, Ontario
PROJECT TITLE / TITRE DU PROJET	Effect of LSD on the neurochemistry of the mammalian brain
YEARS FUNDED / ANNÉES SUBVENTIONNÉES	1976-77
FUNDS ALLOCATED / SUBVENTIONS ASSIGNÉES	$20,000
TELEPHONE NUMBER / NUMÉRO DE TÉLÉPHONE	(416)2843224

FIELD OF RESEARCH / SUJET DE LA RECHERCHE: ☐ EVALUATION / ÉVALUATION ☒ BIOMEDICAL / BIOMÉDICALE ☐ BEHAVIORAL / COMPORTEMENT ☐ SOCIAL SCIENCE / SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY / MULTI-DISCIPLINAIRE

Information on the effect of psychotropic drugs on macromolecular synthesis in the mammalian brain is limited at present. Research on these drugs has concentrated on psychological and physiological aspects. We have sought to determine whether biochemical changes at the level of protein and RNA synthesis occur in the rabbit brain following the intravenous injection of LSD. Massive drug dosages are avoided in our studies. We employ levels which are comparable to those which cause distortion of sensory perception in humans.

In our first report (Brown, 1975) we examined the effect of LSD on transcription in the rabbit brain. We noted that 2 1/2 hours after the intravenous injection of LSD, the ability of isolated brain nuclei to synthesize RNA was increased over saline controls. Both nucleoplasmic and nucleolar RNA synthesis were elevated in cerebral hemispheres and brain stem nuclei. The greatest increase was observed in the latter region which includes the raphe nucleus. LSD is known to specifically affect nerve firing in this region.

Since covalent modification of chromosomal proteins may be prerequisite to a change in gene activity we examined the effect of LSD on actylation of brain histones at a period 30 minutes after drug administration (Brown & Liew, 1975). A stimulation in the acetylation of total histones in cerebral hemisphere and brain stem nuclei was noted. Evidence for the stimulation of acetylation in individual histone bands was obtained after separation by electrophoresis on polyacrylamide gels. Histones in thebrain stem demonstrated the greatest increase in acetylation.

LSD exerted a striking effect on the protein synthesis apparatus of the brain (Holbrook & Brown, 1976). The drug induced a marked disaggregation of polysomes in 3 major brain areas after 30 minutes with a gradual return to normal levels by 4 hours. This transient polysome shift was not caused by RNase degradation. During maximal polysome disaggregation there was a measurable decrease in proteinsynthesis. The effect seemed to be brain specific as spleen and kidney polysomes were not affected. We have analyzed the mechanism of brain polysome shift (Holbrook & Brown, 1977a). Decreased reinitiation of protein synthesis rather than premature termination induces the polysome disaggregation. At a constant dosage of 50 ug/kg the degree of polysome shift increases with age from 3 week old rabbits to adults. There is a disaggregation of fetal brain polysomes when LSD is administered maternally. Elements of environment and physiological arousal were involved in the macromolecular effect of the drug on the protein synthesis apparatus of the brain.

LSD is known to interact with neurotransmitter receptors for biogenic amines, thereby affecting adenylate cyclase and in turn cytoplasmic levels of cyclic AMP. We have shown that neurotransmitter receptors are involved in the effect of LSD on brain polysome disaggregation. Administration of of neurotransmitter receptor blockers prior to LSD eliminated the polysome shift (Holbrook & Brown, 1977b).

These studies are of significance at two levels. First they supply new information on how a psychotropic drug affects basic brain metabolism. Secondly LSD simulates some of the symptoms of schizophrenia and associated psychiatric illnesses. The antipsychotic agents chlorpromazine and haloperidol are used to treat LSD overdoses and for therapeutic maintenance of schizophrenic patients. These agents were found to prevent LSD-induced brain polysome shifts in rabbits. The macromolecular changes in the brain which we have observed following LSD administration may be of some relevance to events in the etiology of naturally occurring psychiatric illnesses

Publications

1) Brown. I.R. (1975). RNA synthesis in isolated brain nuclei after administration of LSD in vivo. Proc. Nat. Acad. Sci. 72, 837-839.

2) Brown, I.R. & Liew, C.C. (1975). LSD: Effect on histone acetylation in rabbit brain. Science, 188, 1122-1123.

3) Holbrook, L. & Brown, I.R. (1976). Disaggregation of brain polysomes after administration of LSD in vivo. Journ. of Neurochemistry, 27, 77-82.

4) Holbrook, L. & Brown, I.R. (1977). Disaggregation of brain polysomes after LSD in vivo: Mechanism and effect of age and environment. Journ. of Neurochemistry, in press, accepted March 21.

5) Holbrook, L. & Brown, I.R. (1977b). Antipsychotic drugs block LSD induced disaggregation of brain polysomes. in preparation.

Presentations at international meetings

1) Holbrook, L. & Brown, I.R. (1976). Disaggregation of brain polysomes after LSD in vivo. Annual Meeting of the American Society for Neurochemistry, Vancouver, March.

2) Brown, I.R. (1977). Inhibition of brain protein synthesis after LSD: Mechanism and identification of affected proteins.Invited workshop presentation , 6th International Congress of the Society for Neurochemistry, Copenhagen, August.

3) Brown, I.R. (1977). Analysis of gene activity in the mammalian brain. Invited symposium speaker, Satellite Symposium to the Copenhagen congress on Brain Protein Synthesis, Amsterdam, August.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Gilles CAILLE	Pharmacologie, Faculté de Médecine
INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE	
Université de Montréal, Case postale 6128, Montréal, P.Q.	
PROJECT TITLE – TITRE DU PROJET Détermination de la phencyclidine plasmatique et urinaire chez le chien et corrélation avec les CPK sériques.	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES
1er avril 1976 au 1er sept. 1977	$24,862.50

TELEPHONE NUMBER / NUMÉRO DE TÉLÉPHONE: 343-7904

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Buts à court terme

1- Etablir une méthode de dépistage rapide et sensible de la PCP en milieux biologiques, ainsi que de ses métabolites urinaires, l'hydroxy PCP et le dihydroxy PCP.

2- Etablir une corrélation entre les niveaux plasmatiques de la PCP et ceux sériques de la CPK.

3- Construire un modèle cinétique de la PCP chez le chien.

4- Distribution et corrélation morphologique.

Buts à long terme

Etablir une méthode de diagnostic rapide et efficace de l'intoxication aiguë à la PCP grâce à la corrélation PCP/CPK.

Des trois buts proposés lors de notre demande d'octroi, un premier a été réalisé soit la mise au point d'une méthode analytique de la PCP en milieu biologique. En ce qui a trait aux métabolites de cette drogue, ils ont été isolés chez cinq chiens et grâce à la collaboration du docteur Denis Lin de Columbus Ohio et de Monsieur R.A. Graham du Ministère de la Santé Fédéral, nous attendons sous peu les standards qui nous permettront d'évaluer les échantillons en main et de poursuivre le travail déjà commencé. Pour ce qui est de la PCP, après plusieurs tentatives infructueuses quant au choix d'un standard interne adéquat, nous avons choisi l'aminopyrine dont l'extraction du sang se situe à 90 ± 4% et dont le temps de rétention en chromatographie en phase gazeuse est de 5.80 minutes, comparativement à 3.40 minutes pour la PCP. Différentes extractions ont été étudiées et nous avons, après avoir effectué une étude comparative des différents milieux, arrêté notre choix sur le milieu alcalin qui assure une meilleure extraction autant d'un point de vue quantitatif que du côté de reproductibilité de l'extraction. Suite à la mise au point de notre méthode d'extraction et de notre méthode analytique, nous avons entrepris l'étude proposée lors de notre demande et à date, cinq chiens, appartenant au groupe A, ont été réalisés. Les échantillons ont été conservés au congélateur jusqu'à la disponibilité des métabolites que nous devons recevoir sous peu. Les analyses des CPK sont actuellement en marche sur ces cinq chiens et confirment notre hypothèse de travail en ce sens qu'on assiste à une augmentation marquée après administration d'un PCP aux chiens. Trois chiens sont décédés au cours de l'expérience du groupe B et différents tissus ont été conservés pour une étude en microscopie électronique. Au cours de cette période d'une année, deux hôpitaux de Montréal, l'hôpital Maisonneuve-Rosemont et l'hôpital Santa Cabrini, nous ont fait parvenir des échantillons sanguins et urinaires de quelques patients admis à l'hôpital pour intoxication au PCP. Les annexes I et II démontrent les avancés que nous avons faits lors de ce résumé. A la suite de notre étude, les conditions du chromatographe en phase gazeuse ont été fixées comme suit: la colonne est une colonne OV17 3%, 80/100 mesh avec une phase Gas Chrom. Q avec des températures de 240°C pour le four, 300°C pour le port d'injection et de 300°C pour le détecteur. Le débit du gas vecteur a été établi à 60 ± 2 ml/minute.

ⓐ METHODES D'EXTRACTION

Prendre 5ml (duplicata) de chaque fraction A,B,C,D,E,F, pour chacune des 3 méthodes d'extraction.

Extraction en milieu neutre non-tamponne

5ml de solution contenant P.C.P. et S.I.

SOLUTION

Extraire avec 10 ml d'éther

Agiter durant 5 min. Centrifuger

Recueillir l'extrait éthéré

Sécher l'éther avec du Na_2SO_4 anhydre

Evaporer l'éther à sec

Reprendre dans 50 µl de $CHCl_3$

Injecter ± 3 µl dans G.L.C.

Extraction en milieu neutre tamponné

5ml de solution contenant P.C.P. et S.I.

Ajouter 10ml de tampon phosphate pH = 7.2 0.4 M

SOLUTION

Extraire avec 10 ml d'éther

Agiter durant 5 min. Centrifuger

Recueillir l'extrait éthéré

Sécher l'éther avec du Na_2SO_4 anhydre

Evaporer l'éther à sec

Reprendre dans 50 µl de $CHCl_3$

Injecter ± 3 µl dans G.L.C.

Extraction en milieu basique

5ml de solution contenant P.C.P. et S.I.

Ajouter 5 gouttes de NaOH 5 N. Vérifier le pH

SOLUTION

Extraire avec 10 ml d'éther

Agiter durant 5 min. Centrifuger

Recueillir l'extrait éthéré

Sécher l'éther avec du Na_2SO_4 anhydre

Evaporer l'éther à sec

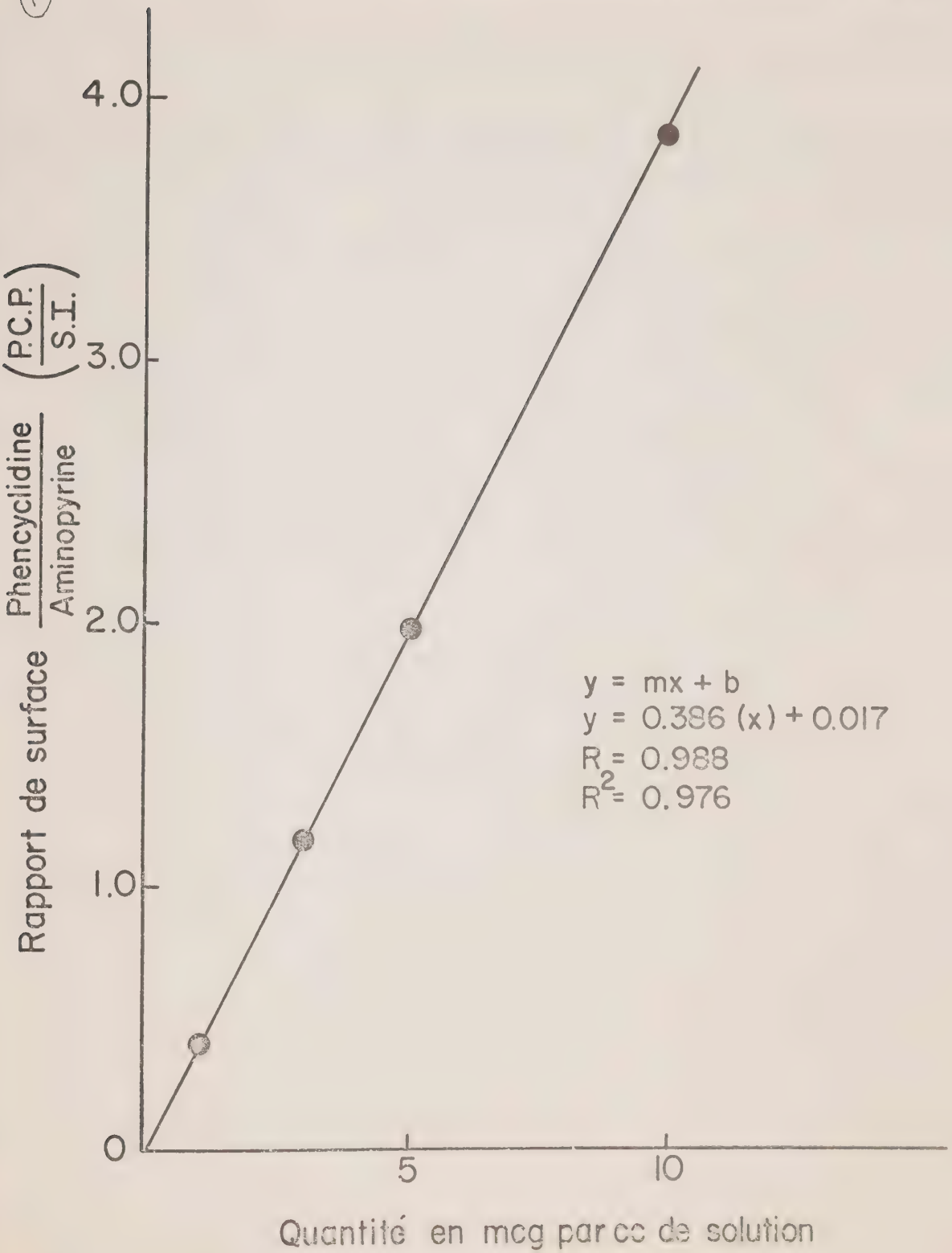
Reprendre dans 50 µl de $CHCl_3$

Injecter ± 3 µl dans G.L.C.

ANNEXE IV

COURBE DE RÉGRESSION (PLASMATIQUE)

(10)



Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
DR. DONALD J. ECOBICHON	PHARMACOLOGY

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE

FACULTY OF MEDICINE, DALHOUSIE UNIVERSITY, HALIFAX, N. S.

PROJECT TITLE The placental and milk transfer of chronic low-doses of methadone its pharmacokinetics and effects on morphological and biochemical aspects of hepatic function in the neonatal guinea pig.

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1976-1978	$42,520	902-424-2562

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMÉDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The extensive use of methodone (street as well as maintenance programmes) has increased the number of pregnant women receiving this agent. In addition to the difficult treatment of withdrawal symptoms, the question has been raised whether methadone might have subtle effects on hepatic enzymes in the developing neonate. Induction of hepatic drug-metabolizing enzymes has been observed in methadone-treated animals. In view of the paucity of good pharmacokinetic studies in humans and the need for an animal model comparable to the human, this research project proposes to (i) investigate the pharmacokinetics of transplacental and milk transfer of methadone in the guinea pigs; (ii) quantitatively study the tissue distribution of methadone in dams and perinatal guinea pigs; (iii) examine perinatal liver for morphological and biochemical changes following receipt of methadone via the placental membranes or via the milk; (iv)investigate the pharmacokinetics of transplacental and milk transfer of chronic low doses of methadone in the perinatal guinea pig from 50 days gestation onward.

In the initial study, non-pregnant female guinea pigs received daily doses of 10 mg methadone/kg, per os, for 7 days. Groups of animals were killed each day, samples of blood, liver and brain being obtained for quantitation of the methadone residues by gas-liquid chromatography, morphological examination of the liver by light and electron microscopy and analysis of biochemical changes of hepatic drug-metabolizing enzymes. Peak blood plasma levels (72±13ng/ml) were reached on day 2, dropped to 40±8ng/ml by day 3 and remained relatively constant for the remaining 6 days. No induction of hepatic drug-metabolizing enzymes (p-nitroanisole O-demethylase, aniline hydroxylase, UDP-glucuronyl-transferase) was observed though from day 3-6 the activities were at the upper limit of the control values, suggesting that the dose was insufficient to cause enzyme induction. Hepatic methadone residues measured 194±54 ng/g after day 2 of treatment and remained relatively constant thereafter. No significant morphological changes were noted in the hepatocytes. This 7-day experiment is being repeated with 25mg methadone/kg doses. The plasma half life ($t_{\beta}/2$) was determined to be 10 and 13.5 hours following single oral doses of 10 and 25 mg/kg respectively.

Following the assessment of the results from the above experiments, pregnant guinea pigs will receive a suitable oral dose of methadone daily from day 50 of gestation until parturition, with animals being killed at day 60, 65 and 68 (term), the tissues of both dams and foeti being removed for chemical, morphological and biochemical analysis. Untreated dams with newborn pups will receive the same daily oral dose of methadone for 14 days in order to study the milk transfer of the agent. Suckling neonates and dams will be killed and tissues removed for chemical, morphological and biochemical analysis.

A final study, based on the results of the above study will involve the chronic administration of a selected dose of methadone to pregnant dams from day 50 of gestation until weaning, killing the dams, foeti and pups at selected intervals for analysis of the effects on perinatal hepatic development and of the pharmacokinetics of drug distribution during pregnancy and lactation.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER - NOM ET SIGNATURE DU CHERCHEUR
Havlicek, Viktor, M.D., D.Sc.

DEPARTMENT - DÉPARTEMENT
Physiology

INSTITUTION AND ADDRESS - ÉTABLISSEMENT ET ADRESSE
Faculty of Medicine, University of Manitoba, 770 Bannatyne Avenue, Winnipeg, Manitoba, R3E 0W3.

PROJECT TITLE - TITRE DU PROJET
Abnormalities of brain electrical maturation of sleep states in newborn infants of chronic alcoholic mothers.

YEARS FUNDED - ANNÉES SUBVENTIONNÉES
1 1/2 years

FUNDS ALLOCATED - SUBVENTIONS ASSIGNÉES
over two years, $43,000.00

TELEPHONE NUMBER - NUMÉRO DE TÉLÉPHONE
204-786-3767

FIELD OF RESEARCH - SUJET DE LA RECHERCHE
[ ] EVALUATION - ÉVALUATION
[X] BIOMEDICAL - BIOMÉDICALE
[ ] BEHAVIORAL - COMPORTEMENT
[ ] SOCIAL SCIENCE - SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY - MULTI-DISCIPLINAIRE

Progress Report

Twenty-six infants of alcoholic mothers or mothers with drinking problems during pregnancy were studied and compared with 26 infants born to healthy nondrinking mothers (controls). Spectral analysis of the EEG using fast Fourier transform showed to be very sensitive tool to detect significant differences between these two groups of infants and to describe a new EEG component of the fetal alcoho' syndrome (Havlicek, Childiaeva, Lancet, 1976, ii, 477). A PDP8/E computer with 16K words of memory located in our laboratory was used to analyze 10.24 second epochs of two channel EEG recordings. The resulting frequency spectra were integrated into eight frequency bands and an overall sum. This greatly reduced data volume and facilitated statistical analysis. One-way and two-way analyses of variances were performed on the University of Manitoba IBM 360/158 after on-line transfer of data through the CDC System 17 based at the Medical College. These data indicate that infants of alcoholic mothers show prominent hypersynchrony in all three stages of sleep of a newborn baby. In quiet sleep "alcoholic" infants differed from healthy babies by significantly higher power in wide range of frequency bands (1.5 - 17.5 Hz) with an average 143% increase of the integrated EEG (1.5 - 25 Hz). In indeterminate sleep "alcoholic" infants showed significantly higher power in all analyzed frequency bands (0.1 - 25 Hz) with an average 196% increase of the integrated EEG (1.5 - 25 Hz). In active-REM sleep infants of alcoholic mothers showed significantly higher power in the frequency range from 0.1 - 17.5 Hz with an average 200% increase of the integrated EEG (1.5 - 25 Hz). The quiet sleep-REM sleep frequency spectrum difference was at term (> 37 weeks gestation) nonsignificant in infants born to alcoholic mothers. All healthy term infants showed significantly higher power in most frequency bands during quiet sleep in comparison with active-REM sleep. EEG hypersynchrony in infants of alcoholic mothers could represent one of the symptoms of the neonatal alcohol-withdrawal syndrome. However this is unlikely since hypersynchrony has been detected as long as 6 weeks after birth. During this time any withdrawal symptoms would have been dissipated.

(continued on next page)

In cooperation with the Child Development Clinic (Director Dr. McRae) infants of alcoholic mothers are examined for morphometric, neurological and intellectual development at following birth ages: six weeks, six months and then at yearly intervals up to school age. Thus abnormalities in the development of electrical activity of the brain will be correlated with subsequent neurological and intellectual development. Since infants of alcoholic mothers show underdevelopment in body growth, in cooperation with Dr. H. Friesen we have started to study levels of growth hormone in blood plasma in these infants. By using all these examinations this project is designed to make early diagnosis of abnormalities in brain development in offspring of alcoholic mothers possible with the ultimate goal to understand the mechanism of such abnormalities. It is hoped that our study will be important in planning specific therapeutic, preventive and educational programs for such infants. Data of this project are being used in the design of preventive and educational programs for alcoholic mothers and eventually fathers also. This seems to be very important since majority of these mothers bear many babies.

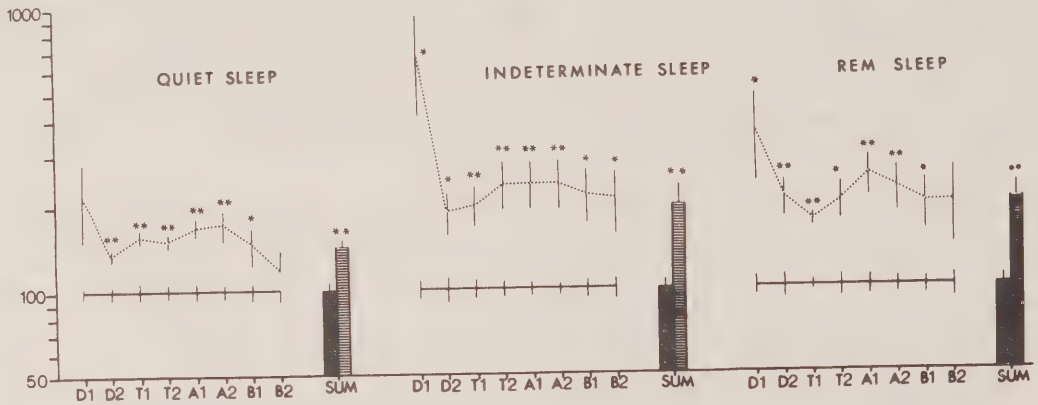


FIGURE 1: Differences in power-spectrum ($\mu V^2/Hz$) between group of healthy infants (indicated by solid line) and the group of infants born to alcoholic mothers (indicated by broken line) during quiet sleep, indeterminate sleep and active-REM sleep. Values of individual sleep stages in healthy infants were taken as 100%. Horizontal scale = frequency bands D1 = 0.10 - 1.48 Hz, D2 = 1.56 - 3.51 Hz, T1 = 3.61 - 5.57 Hz, T2 = 5.66 - 7.52 Hz, A1 = 7.62 - 9.47 Hz, A2 = 9.57 - 12.50 Hz, B1 = 12.60 - 17.48 Hz, B2 - 17.58 - 25.0 Hz, SUM = 1.56 - 25.0 Hz. Vertical lines indicate S.E.; * = $p \leq 0.05$, ** = $p \leq 0.01$ for differences between healthy group and "alcoholic" infants.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR
M. Hirst & C.W. Gowdey M. Hirst C.W. Gowdey

DEPARTMENT – DÉPARTEMENT
Pharmacology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Western Ontario, LONDON, ONtario N6A 5C1

PROJECT TITLE – TITRE DU PROJET
Animal Models of Heroin and Other Opiod Tolerance and Dependence

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1976-77	$99,989	(519) 679-3831

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
☐ EVALUATION – ÉVALUATION
☒ BIOMEDICAL – BIOMÉDICALE
☐ BEHAVIORAL – COMPORTEMENT
☐ SOCIAL SCIENCE – SCIENCES SOCIALES
☐ MULTIDISCIPLINARY – MULTIDISCIPLINAIRE

1. DESCRIPTION OF PROJECT

The major objective of the project is to further investigate a possible model of opiate tolerance and physical dependence based on changes in diurnal feeding patterns and body temperatures, weight changes and irritability during treatment and abstinence, in rats. These changes were investigated initially after chronic administrations of heroin (Thornhill, Hirst and Gowdey, 1976a, b). During the past year other narcotic analgesic analogues and unrelated drugs have been exposed to the model, including morphine, codeine, nalorphine, levorphanol, dextrorphan and amphetamine. A significant technological advance in this preparation has been the introduction of telemetric devices permitting round-the-clock monitoring of core temperatures over prolonged periods. Correlative studies, investigating rat models of psychological dependence based on drinking of opiate-containing solutions and administrations of single doses of long-acting narcotic-containing formulations are being examined. In addition, micro-analytical methods for the detection of narcotic drugs in various biological fluids are being developed.

2. SUMMARY OF RESULTS

Morphine sulphate (5 mg and 20 mg/kg given s.c. at 0800 hrs) behaved like heroin in causing an initial abolition of feeding activity. As injections continued over several days this initial phase of no eating was followed by a period of vigorous feeding which occurred progressively sooner after the injection. Patterns of changes in body temperature occurred which were dependent on dose, the diurnal phase and the duration of drug exposure. Naloxone antagonized these changes in a dose-related manner. Codeine phosphate (40 mg and 200 mg/kg, given s.c. at 0800 hrs) produced similar changes over more prolonged periods which could be antagonized (for about 8 hr) by naloxone (10 mg/kg). Withdrawal from codeine was related in severity to the administered dose and was more marked than in rats receiving morphine sulphate (5 mg, 20 mg/kg) or heroin hydrochloride (5 mg, 20 mg/kg). The rats showed severe hyper-irritability, hypothermia and body weight losses. Nalorphine hydrochloride (5 mg and 20 mg/kg, given daily at 0800 hr) showed slight evidence of opiate agonist effects on feeding activity and core temperature which were antagonized by naloxone pretreatment. Withdrawal from nalorphine was of low severity, there being no noticeable hyper-irritability, no loss of weight and feeding and temperature patterns quickly returned to normal. Amphetamine sulphate (d, ℓ-, 1 and 5 mg/kg, injected s.c. at 0800 hrs and 2000 hrs) produced dose related hyper-thermia, anorexia and sterotypic behaviour. Repeated injection revealed little if any tolerance to these effects over a 10 day treatment period. Withdrawal was associated with voracious feeding. Dextrorphan (2mg and 8 mg/kg, s.c. at 0800 hrs) was without effect whereas levorphanol (2 mg and 8 mg/kg) behaved like heroin and morphine (vide supra). Brief highlights of the companion investigations show that rats treated with heroin (20 mg/kg at 0800 hrs. s.c.) show no preference for drinking a dihydromorphinone solution (0.1 mg/ml) rather than water. Nonetheless, a stimulated phase of drinking occurred in rats which paralleled the above-mentioned stimulated feeding. Injections of heroin zinc tannate (containing 45 mg/kg and 90 mg/kg of heroin) into rats gave a dose-related anorexia and feeding pattern disruption which lasted over several days. Hypophagia was evident after 27 days but the diurnal feeding pattern had returned to normal. In sacrificed animals the injected material was found to be encapsulated and clear of infection at that time.

In our laboratory naloxone-precipitated jumping is a doubtful quantitative assay of narcotic dependence in mice. Similarly, an investigation revealed that changes in sensitivity to thermal nociception during abstinence from heroin did not parallel withdrawal severity. A microanalytical method of dihydromorphinone analysis from human serum has been developed based on GLC-EC analysis. This method is sensitive to picogram quantities of material. Procedures for determinations of morphine in dog and human saliva have proved to be of great sensitivity.

3. SIGNIFICANCE

The results suggest that the rat model may be a sensitive and specific preparation for examining the actions of narcotic agonists. It further serves to monitor long-acting preparations of narcotic agonists which should have experimental and clinical value. Micro-analytical techiques of high sensitivity are of value in detecting narcotic abusers and monitoring laboratory and clinical studies in which these drugs are employed.

4. RELEVANCE

These studies have high potential for addressing the NMUD objectives of reducing the likelihood of fostering dependence on new analgesics by screening through an economical and sensitive preparation, improving methods for identifying narcotic abusers, and, potentially, of introducing narcotic preparations of low dependency profiles for therapeutic use.

5. FUTURE DIRECTIONS

The rat model will be further explored using opiate and non-opiate drugs of varying potencies and actions to further monitor its specificity and to see if the changes that occur are indicative of the abuse potential of the drugs; further investigations of the long-acting narcotic preparation and extensions of the microanalytical techniques to other selected narcotic drugs.

REFERENCES

Thornhill, Hirst and Gowdey (1976a) Pharm. Biochem. Behaviour 4, 129-135

Thornhill, Hirst and Gowdey (1976b) Arch. Int. Pharm. 223, 120-131.

PUBLICATIONS AND COMMUNICATIONS

Brands, B., Hirst, M. and Gowdey, C.W. "Duration of analgesia in mice after heroin by two testing methods". Can. J. Phys. Pharm. 54, 381 (1976)

Brands, B., Hirst, M. and Gowdey, C.W. "Analgesia duration and physical dependence in mice after a single injection of three heroin salts and morphine sulphate in various vehicles" Arch. Int. Pharm. (submitted)

Hirst, M., Herne, R.G. and Robinson, J.R. "A rapid method for microdetermination of morphine in human biological fluids by electron-capture gas-liquid chromatography" Clin. Chem. (submitted).

Hirst, M., Thornhill, J.A. and Gowdey, C.W. "Inhibition of morphine-induced hyperthermia in rats by naloxone pretreatment". Pharmacologist 18, 177 (1976)

Thornhill, J.A., Hirst, M. and Gowdey, C.W. "Effects of repeated injections of heroin on diurnal temperature and feeding patterns in rats". Proc. Can. Fed. Biol. Soc. 19 1 (1976).

Herne, R.G., Hirst, M. and Gowdey, C.W. "A sensitive gas-liquid chromatographic method for analyses of hydroxyphenathocal opiates in biological fluids". Proc. Can. Fed. Biol. Soc. 19, 46 (1976).

Thornhill, J.A., Hirst, M. and Gowdey, C.W. "Lack of tolerance development in rats to the anorexigenic and hyperthermic effects with repeated injections of d, ℓ-amphetamine" Can. J. Phys. Pharm. (submitted).

Thornhill, J.A., Hirst, M. and Gowdey, C.W. "Temporal shifts in responses of hyperthermia and hyperactivity with repeated low doses of morphine in rats". Pharm. Biochem. Behaviour (in preparation)

Thornhill, J.A., Hirst, M. and Gowdey, C.W. "Alteration by naloxone of temperature responses to saline and morphine in the rat". Can. J. Phys. Pharm. (in preparation).

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
E.A. HOSEIN	Biochemistry

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
McGill University, 3655 Drummond St. Montreal H3G 1Y6

PROJECT TITLE – TITRE DU PROJET
Assessment of Cellular Damage Subsequent to Acute and Chronic Opiate Administration and during

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1975,76,77	$25,000	514 392-3019

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION
[X] BIOMEDICAL BIOMÉDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Since the review of this application a few months ago a number of experiments have been carried out, which have yielded some interesting results. They are summarized under three headings.

(i) Treatment of rats with various doses of morphine have established that a dose response relationship exists for many of the parameters previously studied.

(ii) In previous work, oxilorphan reversal of agonist activity was studied in some detail. We now have data which underlie opiate specificity since blockade was reversed by low doses of the pure antagonist naloxone and the longer acting oxilorphan. We have also shown that minute amounts of leucine enkephalin *in vitro* can mimic an *in vivo* morphine effect on membrane lipids.

(iii) We have isolated ether precipitable material from membrane lipids whose properties are responsible for the induction of opiate effects in membrane lipids both *in vivo* and *in vitro*; effects which are abolished by naloxone. Identification of this material as the opiate receptor is being sought.

Previous work showed that 40 minutes following the *in vivo* administration of morphine (2.5, 5 or 10 mg/kg i.v.; 50 or 100 mg/kg i.p.) to rabbits there was a dose response relationship on the percentage of erythrocytes whose biconcavity index was changed from 0.75 to 1, due to induced changes in membrane geometry. This effect was reversed by 1 mg/kg naloxone. It was also observed that 0.5 hr after an acute dose of 25 mg morphine/kg was injected i.p. to rats, the activity of a number of enzymes embedded in the inner mitochondrial membrane or the synaptosome was decreased. When the assays were carried out after a latent period of 48 hrs post-opiate, there was an increase in the activity of these membrane bound enzymes. Soluble (matrix) enzymes were unaffected, indicating that the effect was specific for membrane bound enzymes. Arrhenius plots of these membrane bound enzymes showed a phase transition temperature of 18.5°C for the membrane lipids in the controls while the value for morphine treated animals was 16°C, indicative of increased membrane fluidity and disorder. This effect was reversed by 1 mg naloxone or oxilorphan/kg i.p. 0.25 hr post-opiate. Samples from animals after a latent period of 48 hrs post-opiate, showed an increase in the phase transition temperature to 20.5°C indicative of increased order and stabilization of the membrane lipids. The question therefore arises as to the permanence of this effect. That is, whether the effect on the membrane components, structure and/or function is reversible after periods of latency (acute) or withdrawal (chronic). The factor(s) responsible fdor the induced alteration in membrane lipids will be sought as they may well be responsible for the development of long term tolerance following acute morphine administration. The fact that after a 48 hr. latent period (when presumably there is little or no morphine present in the brain) there is both an increase in enzyme activity and a decrease in membrane lipid fluidity, further suggest a fundamental role for membrane lipids in the latent action of morphine.

When these experiments with Arrhenius plots were repeated with crude brain mitochondrial fractions from rats which had received chronic morphine for 7 days, tolerance to the drug

could be assessed (in samples taken 0.5 hr post-opiate) by a gradual decrease in the inhibition of the activity of inner mitochondrial or synaptosomal enzymes. The lower phase transition temperature remained at 16°C. Correspondingly, samples assayed 48 hrs post-opiate in dependent animals, showed increased enzyme activity with the same increased phase transition temperature of 20.5PC found with acute animals. It is proposed to repeat thse acute and chronic experiments with smaller doses of morphine, levorphanol and (inactive) dextrophan to determine the minimum dosage of these enatiomorphs which would induce these effects and to test the efficacy of this reversibility by naloxone.

Since a decrease in phase transition temperature of a membrane bound enzyme is indicative of early melting of lipid in its microenvironment and the opposite holds for an increase, we have determined the melting profile of these membrane lipids with the differential scanning calorimeter (DSC). In general, we found that lipids from the crude mitochondrial fraction from morphine treated rat brains had identical (initial) T_i of -17°C with that of controls, but (final) T_f were different from each other. The value for the extract from naive animals was +17°C indicative of the naive (N) state of the membrane lipids, and -1°C indicative of the morphinized (M) state of the membrane lipids in animals harvested 0.5 hr after treatment. This (M) effect which is dose dependent was reversed by the administration of naloxone or oxilorphan to morphinized rats. *In vitro* addition of either 5 nM morphine or 20 µM leucine enkephalin per mg lipid extract from naive rats, produce the *in vivo* (M) effect which was reversed by 5 nM naloxone or oxilorphan *in vitro* to produce the (N) scan once more. Addition of ether to the lipid extract from the morphine treated rats caused precipitation of a material whose removal abolished the (M) effect from the extract. The (M) effect was restored on addition of the precipitate to the supernatant. Mixing the ether precipitate from naive animals with the supernatant from morphinized animals restored the (N) profile. Mixing the morphine precipitate with the naive supernatant gave the (M) profile. The ether precipitate from the morphinized extract clearly was unique in this property to produce the (M) profile and might be identified with the opiate receptor. The question arises as to the fundamental nature of the (M) precipitate in the action of morphine *in vivo*. Certain investigators have shown that cerebrosides are precipitable from brain lipid extracts by ether and others have identified cerebroside sulphate with the opiate receptor. The matter of the identity of the opiate receptor, however, is as yet unresolved because other investigators have suggested that it might be a protein. Comparison of the stereospecific binding of cerebroside sulphate (which has a peptide bond as part of its structure) and the ether precipitable material with ^{14}C morphine, levorphanol and (inactive) dextrophan and its reversal with naloxone or oxilorphan will be carried out. Lipid extracts of discrete areas of the brain where there is known to be high receptor density will be prepared from normal and morphinized animals and the DSC scan compared with that produced with the crude brain mitochondrial extract.

The other phase of this work concerns the DSC profile of membrane lipids extracted 48 hrs post-opiate. While the T_i is identical with the naive extract, the T_f +27°C indicative of a latent (L) effect of the opiate in the membrane lipids is greater than that obtained with morphinized or naive naimals. This effect is also produced in naive lipid extracts (N) on the *in vitro* addition of 3 mM Ca^{2+}. It is proposed to identify the factor in the 48 hr lipid extract which produces this (L) effect because it might reveal (i) how the biphasic effect of the drug is manifested and (ii) the role of Ca^{2+} in the action of opiates.

In addition to the above, the *in vitro* interaction of naloxone, sodium and manganese ions with the various ether precipitates, will also be carried out. Whether or not morphine is found to be present in the (M) precipitate will also be determined.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DEPARTEMENT
Kalow, Inaba, Kalant T. Inaba	Department of Pharmacology
INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE	
University of Toronto, Toronto, Ontario M5S 1A8	
PROJECT TITLE TITRE DU PROJET	
Cocaine Disposition and Tolerance	
YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES / TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1976-1977	$20,000 / (416) 978-2723

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☒ BIOMEDICAL BIOMEDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Research Project

The purpose of the proposed study is to provide the scientific basis for an understanding of the central nervous system effects of chronic cocaine use and for appropriate medical action in users of cocaine. Optimal medical action requires a full understanding of the inter-relationship between drug and human being, that is, not only of the action of the drug on the body, but also the action of the body on the drug. This knowledge is a prerequisite for the interpretation and understanding of drug-drug interactions, the extent of person-to-person differences in drug elimination, changes of drug elimination in a given individual through exposure to other chemicals, the effects of pathology of liver or kidney, or various kinds of adaptation phenomena. In short, the purpose of this study is to provide a presently missing comprehension and understanding without which any approach to therapy must be empirical but cannot be fully rational.

Key findings made so far will appear in Life Sciences shortly (May 77). The paper is entitled "Hydrolysis of Cocaine in Human Plasma by Cholinesterase" by D.J. Stewart, T. Inaba, B.K. Tang and W. Kalow.

As a first step towards studying cocaine metabolism in humans, we examined plasma for cocaine hydrolyzing activity. Human plasma has mainly two esterases, cholinesterase (EC. 3.1.1.8) and aromatic esterase, which are known to hydrolyze drugs and could contribute to the elimination of cocaine. Some investigators have already examined human plasma and found no evidence of enzymatic hydrolysis of cocaine. They were, however, using extremely high cocaine concentrations. In this study, we used a cocaine concentration more comparable to that measured in human plasma after drug exposure. We find that there is indeed enzymatic hydrolysis of cocaine and have demonstrated that the enzyme responsible is cholinesterase.

In Summary,

hydrolysis of cocaine to ecgonine methyl ester in human plasma is mediated by cholinesterase. Cocaine hydrolysis by plasma is blocked by DFP and eserine and partially inhibited by fluoride. Highly purified cholinesterase from human plasma when diluted to the same benzoylcholine hydrolyzing activity as human plasma, shows the same rate of cocaine hydrolysis as human plasma. There was no detectable enzymatic conversion of cocaine to benzoyl ecgonine in plasma.

Significance, Relevance, Future Directions

Recently the abuse of cocaine has been rising in spite of its high cost. Valanju et al (1973) discovered the cocaine metabolite benzoylecgonine in 15% of 1000 randomly selected urines from a drug abuse treatment programme in New York City. Police seizures of illicit cocaine in Canada have risen sharply in the last few years. This means that cocaine-related medical problems can be expected to increase also in Canada. The long-term objective of the project is to develop an understanding of the distribution and metabolic fate of cocaine in the human body and of the effects of repeated use.

In one part of these studies, we intend to examine the metabolism of cocaine to norcocaine by N-demethylation in the human and the rat. Norcocaine is a potentially important metabolite that is formed in the liver, brain and possibly the intestine of the rat. There is evidence that this metabolite is as active on the brain as cocaine and may play a role in the toxic effects of cocaine on the liver. In the rat, we are to determine whether microsomal enzyme induction by barbiturates or alcohol can increase the formation of norcocaine. The role of the gut in cocaine metabolism is also to be evaluated. In a limited number of human subjects we intend to evaluate the role of N-demethylation in cocaine metabolism and whether cocaine administration by the oral route can increase the amount of N-demethylation of cocaine.

Another, part of the inquiry into cocaine metabolism will yield an assessment of the relative importance in man of hydrolysis by plasma cholinesterase on the one hand and of oxidative reactions, particularly the demethylation which yields norcocaine on the other hand. The set of kinetic constants to be obtained in vitro will quantitatively indicate cholinesterase interaction with cocaine and with norcocaine, and it will provide these constants for several hereditary variants of cholinesterase. This will permit predictions whether or not one has to expect special susceptibilities to cocaine intoxication in subjects with these enzyme variants.

In the third part of these studies, we will continue our examination of the effects of chronic cocaine exposure on rat behaviour and of the development of cross tolerance between cocaine and amphetamine. In these studies we will evaluate the role of CNS changes and metabolic changes in the development of tolerance.

The availability of the analytical methods and the understanding of the time course of cocaine elimination in terms of pharmacokinetics, may help to unravel some of the complexities associated with the illicit use of cocaine. Among these is the question of tolerance in human users of cocaine. Animal studies have, almost without exception, indicated that repeated administration of initially-tolerated doses leads to increasing sensitivity, often with lethal convulsions. In contrast, clinical observations support the idea of acquired tolerance in regular users. The discrepancy may be attributable to the facts that (1) most animal studies have begun with large doses and escalated the dosage rapidly, and (2) observations in animal studies have centered chiefly on convulsions or respiratory depression, rather than on the more subtle behavioural effects for which humans presumably employ the drug non-medically.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER - NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DÉPARTEMENT
A.W. MacLean A.W. MacLean	Department of Psychology
INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE	
Queen's University, Kingston, Ontario K7L 3N6	
PROJECT TITLE - TITRE DU PROJET	
The Effects of Alcohol on Sleep	
YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES
1973-1977	$92,216

TELEPHONE NUMBER - NUMÉRO DE TÉLÉPHONE 613-547-2697

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION
[X] BIOMEDICAL BIOMEDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Ethanol and Caffeine: Effects on Sleep

J. Cairns and A.W. MacLean
Queen's University, Kingston, Ontario, Canada

As part of a series of studies examining the effects of ethanol on sleep we have recently investigated the combined effects of ethanol and caffeine on the sleep cycle. During acute administration ethanol is generally found to decrease REM sleep, increase REM latency, increase SWS, decrease sleep onset latency and decrease wakefulness following sleep onset. Depending on the dose these changes may only be observed during the first half of the night and may be followed by a rebound in the second half. Caffeine has been found to decrease total sleep time, increase sleep onset latency, increase the amount and number of arousals following sleep onset and decrease SW and REM sleep.[1]

Eight male, paid, volunteer subjects of average age 21 years were adapted to the laboratory for one night. They then experienced all factorial combinations of placebo vs. 1 gm./kg. ethanol and placebo vs. 5 mg./kg. caffeine added to 1.5 gm. decaffeinated coffee. Ethanol was administered at 22.30, caffeine at 23.20, lights out was at 23.45 and lights on was at 07.15. Subjects were assigned to treatments by a balanced latin square; seven nights intervened between each night.

	Placebo		Ethanol	
	Placebo	Caffeine	Placebo	Caffeine
Sleep Onset Latency[c]	18.6	34.1	19.4	29.9
Total Sleep Time[c]	428.4	396.2	409.1	401.7
Total Stage Changes[c,e]	72.5	61.6	64.9	55.8
Mins. REM in 5 hr.[e]	50.3	51.2	35.9	42.2
Mins. SWS in 5 hr.[e]	55.9	59.9	73.8	65.4
No. symptoms in a.m.[e]	5	5	13	9

c,e Statistically reliable effect of caffeine (c) or ethanol (e).

Preliminary analysis of the results indicates that ethanol reliably decreases the total number of stage changes, decreases the number of minutes of REM in 5 hours sleep and increases the amount of SWS in 5 hours sleep. Caffeine reliably increases the sleep onset latency, decreases the total sleep time and decreases the total number of stage changes. No reliable interaction effects have been observed. However, inspection of the data indicates that, with respect to sleep onset latency, total sleep time, minutes of REM in 5 hours sleep, minutes of SWS in 5 hours sleep and number of symptoms checked the following morning, the caffeine-alcohol combination produces results intermediate between those of caffeine alone and alcohol alone.

It may be inferred, therefore, that with respect to at least some measures of sleep, caffeine acts so as to oppose the effects of alcohol.

The above represent our preliminary findings and we are currently extending the size of the subject sample. We are also continuing our investigations of the effects of congeners and the effects of ethanol upon the sleep of alcoholic patients.

1. Kay, D.C. et al. Human Pharmacology of Sleep. In Williams, R.L. and Karacan, I. Pharmacology of Sleep. 1976.

I. Mazurkiewicz - Kwilecki

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DEPARTEMENT
I.M. Mazurkiewicz-Kwilecki	Department of Pharmacology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE

Faculty of Medicine, Univ. of Ottawa, 275 Nicholas Street, Ottawa, Ontario K1N 9A9

PROJECT TITLE - TITRE DU PROJET

Pharmacological Studies on Mandrax and Methaqualone

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1973-1975		231-4078

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☒ BIOMEDICAL BIOMÉDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The effect of Mandrax and its components on brain histamine and histidine decarboxylase activity.

Acute treatment with Mandrax (MA) or with its active components methaqualone (MTQ) or diphenhydramine (DIPH) resulted in alterations in the hypothalamic histamine concentration. The effects of MA and MTQ but not of DIPH were attenuated after chronic treatment with a steady dose of MA, but were noticeable again when MA was administered chronically in increasing doses. The observed changes were reversible after MA withdrawal.

Histidine decarboxylase (HD) activity in the hypothalamus remained unchanged after acute treatment with MA, MTQ or DIPH. However, a significant increase in the activity of this enzyme was noted in the cortex after MA and MTQ administration; DIPH induced only a slight and non-significant increase. Chronic (18 days) daily treatment with MA or DIPH induced a significant increase in the hypothalamic HD activity. A slight (11%) non-significant decrease in the activity of this enzyme was noted after MTQ treatment.

A significant increase in HD activity was also observed after chronic treatment with MA or DIPH in the cortex. MTQ induced a significant decrease in HD activity in this brain region.

The increase in HD activity noted after chronic MA administration in the hypothalamus and cortex seems to be partly due to the DIPH component of this drug which also significantly lowered histamine content in this brain region. The increased HD activity noted after DIPH could have been due to the antihistaminic effects of this drug on the "histaminergic receptors" which could initiate a feedback mechanism. The synergistic effects of DIPH with other central nervous system depressants such as tranquillizers and alcohol were repeatedly reported (1) indicating a possible role of histamine in the mechanism of action of these drugs.

The significant decrease in HD activity in the cortex after chronic MTQ treatment is in line with the reported (2) decrease of brain histamine turnover after acute administration of other types of sedative hypnotics such as barbiturates.

On the basis of the present data it is suggested that brain histamine may be involved in the mechanism of action of these drugs of dependence. These observations are in line with our previous reports (3) on the possible role of brain histamine in morphine dependence and withdrawal. Our preliminary studies indicated that histamine precursor histidine which is one of the aminoacids contained in our diet may influence some of the effects of drugs of abuse (4). This observation may open new vistas for the possible treatment and/or prevention of the undesirable side effects of many clinically useful drugs.

Cont'd .../2

1. K.I. Melville (1973). In "Histamine and Antihistamines", Ed. M. Schachter, Pergamon Press, p. 113.

2. H. Pollard, S. Bischoff and J.C. Schwartz (1974). J. Pharmacol. 190, 88.

3. I.M. Mazurkiewicz-Kwilecki and R.W. Henwood (1976). Agents and Actions 6/4, 402.

4. R.W. Henwood and I.M. Mazurkiewicz-Kwilecki (1976). Can. Fed. Proc. 19, 671.

Health and Welfare Canada Santé et Bien-être social Canada

I.M. Mazurkiewicz-Kwilecki D.A.V. Peters

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
I.M. Mazurkiewicz-Kwilecki and D.A.V. Peters	Department of Pharmacology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Faculty of Medicine, Univ. of Ottawa, 275 Nicholas Street, Ottawa, Ontario K1N 9A9

PROJECT TITLE – TITRE DU PROJET
Pharmacological Studies on Mandrax and Methaqualone

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNEES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1973 - 1975		231-4078

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[X] BIOMEDICAL – BIOMÉDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[ ] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

The acute effects of Mandrax (MA), Methaqualone (MTQ) and Diphenhydramine (DIPH) on 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in various brain regions of the rat.

Mandrax is a combination of methaqualone and diphenhydramine in a ratio of 10:1. Dose response studies were conducted with Mandrax (27.5 mg/kg to 165 mg/kg) and with the corresponding doses of methaqualone (25 mg/kg to 150 mg/kg) and diphenhydramine (2.5 mg/kg to 15.0 mg/kg).

Diphenhydramine (DIPH)

In the midbrain and pons-medulla, oral administration of DIPH produced a dose-dependent decrease in 5-hydroxyindoleacetic acid (5-HIAA) and a corresponding increase in 5-hydroxy-tryptamine (5-HT). This is consistent with a marked decrease in 5-HT turnover in the midbrain, a region known to contain predominantly the cell bodies of the brain serotonergic neurons. In contrast, the 5-HT and 5-HIAA levels in cortex and striatum showed no marked or consistent changes after DIPH treatment. The effect of DIPH on hindbrain 5-HT and 5-HIAA levels appeared to be biphasic since at the highest dose of DIPH used there was little evidence of a decreased turnover.

Methaqualone (MTQ)

MTQ had no apparent effect on 5-HT and 5-HIAA levels in any of the brain regions studied.

Mandrax (MA)

MA administration (27.5 mg/kg to 82.5 mg/kg) produced no consistent pattern of changes in 5-HT and 5-HIAA levels in any of the brain regions studied. This was unexpected since one component of MA, DIPH, produced quite marked alterations in both of these indoles in equivalent doses. However, it is possible that the 10 fold greater amount of MTQ present in MA interferes with the absorption or transport of DIPH into the CNS.

The highest dose of MA (165 mg/kg) investigated produced a significant increase (89%) in the 5-HIAA concentration in pons-medulla which is consistent with an increased 5-HT turnover. At this dose level MTQ only slightly decreased 5-HT turnover.

The present data suggest that the pharmacological properties of Mandrax may in part be due to DIPH component of this drug.

I. Mazurkiewicz - Kwilecki

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
I.M. Mazurkiewicz-Kwilecki	Department of Pharmacology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

Faculty of Medicine, Univ. of Ottawa, 275 Nicholas Street, Ottawa, Ontario K1N 9A9

PROJECT TITLE – TITRE DU PROJET

Pharmacological Studies on Mandrax and Methaqualone

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1973-1975		231-4078

FIELD OF RESEARCH – SUJET DE LA RECHERCHE

[ ] EVALUATION – ÉVALUATION
[X] BIOMEDICAL – BIOMEDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[ ] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Cardiovascular Studies In Vivo

Mandrax (MA) is a combination of methaqualone (MTQ) and diphenhydramine (DIPH) in a ratio of 10:1. In preliminary experiments, acute administration of MA (27.5 mg/kg to 82.5 mg/kg) to non-anesthetized rats induced significant hypotensive effects which were noted 60 min. after oral administration. These effects were less marked after the largest dose (82.5 mg/kg). The hypotensive effects of MA were associated with a significant decrease in the heart rate which seemed to be dose dependent.

Further studies on acute effects of MTQ and DIPH will elucidate which of the MA components are responsible for the cardiovascular effects noted presently. The mechanism of these effects will be explored in order to establish direct or indirect cardiac effects. Chronic studies will be carried out with MA, MTQ and DIPH in order to see whether aggravation or attenuation of cardiovascular effects may occur after the chronic use of these drugs. These studies will bring more information on the mechanism of the toxic cardiac effects reported clinically after overdosage with these drugs and consequently lead to more logical pharmacological basis of the treatment.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER NOM ET SIGNATURE DU CHERCHEUR
Edith G. McGeer

DEPARTMENT – DÉPARTEMENT Psychiatry, Division of Neurological Sciences

INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE
University of British Columbia, Vancouver, B. C., V6T 1W5

PROJECT TITLE TITRE DU PROJET
Effects of methadone on male sexual function and viability of progeny.

YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1976-1977	$37,500 (18 months)	(604)-228-2481

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION
[X] BIOMEDICAL BIOMÉDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Methadone is a potent narcotic which is taken in large doses over a prolonged period of time in the maintenance program for the treatment of persons formerly dependent on heroin. According to clinical reports, dl-methadone has many side effects, as for example, decreased sexual interest, impaired sex organ function, impotency, constipation, and probably a reduced plasma testosterone levels in humans and in animals. Moreover, methadone causes regressive changes in male sex accessory organs and testes of mice. Among the possible side effects, therefore, of the narcotics are actions on the pituitary-hypothalamic-gonadol axis and/or direct effect on gonadol function and steroidogenesis.

Many studies have confirmed that the analgesic activity of the l-isomer of methadone is up to 50 times higher than that of the d-isomer. Little has been reported, however, on the comparative cellular and biochemical effects of the racemate and of the separated optical isomers of methadone.

The objective of these experiments was to investigate:

a) the possible direct effect of methadone on various cellular metabolic and biosynthetic processes; and

b) the comparative effect of dl-, l- and d-methadone on these processes.

In order to exclude the complicated in vivo hormonal relationships, the effect of the narcotic on the rat spermatogenic cell metabolism was studied in vitro.

dl-Methadone at 10-100 μM inhibits in dose related fashion, the incorporation of L-[1-^{14}C]-leucine into the protein of testical cells. Similar dose-related inhibitory effects of the methadone racemate were apparent on both RNA and DNA synthesis, as measured by the incorporation of [$^{14}CH_3$]-thymidine, respectively. Moreover, the results indicate an interference with the synthesis of phosphorylated nucleotides of both labelled uridine and thymidine.

When the relative effects of the separated isomers were compared with that of the racemate, the d- and l-isomers were approximately equal in activity but the dl-mixture was always more inhibitory than either of the separated isomers at the same molar concentration. These results are consistent with the reports of in vivo animal studies indicating that dl-methadone is more toxic than the separate isomers. The effective inhibitory dose of dl-methadone in these in vitro experiments is of the same order of magnitude as the concentrations of methadone and its metabolites found post mortem in human blood.

The results obtained in the present in vitro experiments indicate that: a) methadone has direct inhibitory effects on vital biosynthetic processes in spermatogenic cells; the reported decrease of testerone levels and related sexual problems may be related to

these effects; b) The d-isomer is comparable to the l-isomer in its cellular toxic effects, although it is far less active in the pharmacological action on CNS receptor sites. The results, therefore, strongly suggest the introduction for pharmacological use of only the l-isomer. It should have its pharmacological effects at about half the dose of the racemic mixture and have far less intracellular toxic effects. This may be particularly important during pregnancy in order to minimize toxic effects on the fetus of the mothers on methadone maintenance therapy.

Further studies will be aimed at studying the comparative cellular toxic effects of methadone, l-α-acetylmethadol (LAM-the new, recently clinically introduced substitute of methadone), morphine and heroin. Rats of various ages at different levels of sexual development will be used. Moreover, the distribution and accumulation of labelled methadone in testes and spermatogenic cells, prostate and seminal vesicles as compared to that in other organs will be studied.

Publications:

Jakubovic, A., McGeer, E. G., and McGeer, P. L. Inhibition of cell metabolism by d- and l-methadone or morphine in vitro. Abstracts Eight Annual Meeting, American Society for Neurochemistry, Denver, Colorado, March 13-18, 1977.

Jakubovic, A., McGeer, E. G., and McGeer, P. L. Comparative inhibition of biosynthetic processes in rat testicular cells by d-, l- and dl-methadone. Biochemical Pharmacology (in press).

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER / NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
John P. J. Pinel	Psychology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of British Columbia, Vancouver, B.C. V6T 1W5, Canada

PROJECT TITLE – TITRE DU PROJET
Repeated administration of convulsive agents and the alcohol withdrawal syndrome

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER / NUMÉRO DE TÉLÉPHONE
2 years	$44,000	604-228-4656

FIELD OF RESEARCH / SUJET DE LA RECHERCHE: [ ] EVALUATION / ÉVALUATION [X] BIOMEDICAL / BIOMÉDICALE [ ] BEHAVIORAL / COMPORTEMENT [ ] SOCIAL SCIENCE / SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY / MULTI-DISCIPLINAIRE

Previous attempts to identify factors which predispose individuals to "alcoholism" have concentrated exclusively on inherent genetic, physiological, biochemical, and personality variables. We have considered the possibility that certain external factors may be capable of transforming a "normal" organism into one which is extremely susceptible to at least some of the adverse consequences of alcoholism. More specifically, our hypothesis was that various forms of convulsive "therapy" might produce enduring increases in the susceptibility to the convulsive effects of alcohol withdrawal. This hypothesis was based on reports that repeated, periodic administration of convulsive agents can lead to a progressive and enduring increase in the susceptibility to seizures. This kindling phenomenon has been demonstrated with a variety of agents in a variety of species.

When periodic electroconvulsive shocks were administered to rats, there was a progressive increase in the severity of the motor seizure pattern. This kindling effect was observed when current intensities of 15 or 75 mA were administered at 3-day, but not at 1-hr, intervals. The magnitude of the increase in severity of the motor seizure pattern was a function of the number of electroconvulsive shocks; the effect was asymptotic in these experiments when ten or more stimulations were administered.

Periodic electroconvulsive shocks were also found to potentiate the consequences of subsequent alcohol withdrawal. Following the series of ECSs, each rat was intubated with intoxicating aqueous solutions of alcohol at 8-hr intervals for 2 weeks. Following the last intubation, the incidence of various convulsive withdrawal symptoms was assessed. In general, those factors which were found to potentiate the kindling of electroshock convulsions (i.e., number of electroconvulsive shocks and the intervals between them) had comparable effects on the intensification of the alcohol withdrawal syndrome. This potentiation of the alcohol withdrawal syndrome persisted for at least 3 weeks following ten electroconvulsive shocks administered at 3-day intervals. Finally, the intensification of the alcohol withdrawal syndrome was observed to occur even when the electroshock convulsions had been pharmacologically blocked, as they are during routine clinical application.

These experiments clearly establish that periodic electroconvulsive shocks can produce kindling-like effects and intensify the convulsive consequences of subsequent alcohol withdrawal. We have shown in other experiments that kindling with electrical stimulation of the amygdala or with i.p. injections of Metrazol can produce similar increases in the incidence of alcohol withdrawal symptoms.

Although the results of these experiments can not be applied indiscriminately to human clinical situations, they do suggest that, until the appropriate clinical studies have been performed, the use of potentially convulsive agents by patients following electroconvulsive therapy should be carefully controlled.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
R.E. Rangno, M.D.	Clinical Pharmacology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4

PROJECT TITLE – TITRE DU PROJET
Non-Medical Use of Drugs in Suicidal Overdose: Research Into Some Problems

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
☐ EVALUATION – ÉVALUATION ☒ BIOMEDICAL – BIOMEDICALE ☐ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

1. Brief Description of Research Project

One aspect of drug abuse which is a major public health problem but which has had insufficient, integrated, in depth research, is drug overdose. An audit of this problem by our group has identified three priorities to which we have begun a strategy of investigation. (1) The effect of severe drug overdose on cardiovascular function and the effect of correcting these abnormalities on drug disposition and the clinical course. Hypotension secondary to decreased cardiac output should be corrected rapidly and specifically to enhance hepatic and renal clearance of drugs. Throughout the patients treatment course, using relatively non-invasive techniques, we will study cardiac output as a function of cardiac inotropy and venous return: the latter as influenced by blood volume and venous compliance. A smaller, more detailed study will assess hepatic clearance of drugs as a function of liver blood flow. (2) The effect of ethanol interaction with commonly used drugs on the kinetic disposition of the drugs and the clinical course. We have completed a pharmacokinetic analysis of the interaction of ethanol with common drugs in volunteers and in patients with severe drug-ethanol overdose to establish the mechanism of this theoretical life-threatening potentiation phenomenon. (3) The effect of gastric instillation of large amounts of activated charcoal on drug absorption and the clinical course. We have compared the patients course and the clearance of the drugs after double-blind treatment with either activated charcoal or placebo. The information from these three studies will be inter-related and new treatment methods devised and implemented. The results of that audit will be used to educate the medical community.

2. Summary of Key Findings

Part I. We have shown that the decrease in blood pressure in severe drug overdose is at least in part due to increased venous capacitance. This decreased venous tone probably results in venous blood pooling with decreased return to the heart and thence decreased cardiac output. The safest, most rapid means of correcting this problem is to expand the circulating volume with crystalloid and/or colloid solutions. Studies on the effect of altered liver blood flow on drug clearance are in progress.

Our detailed prospective studies in suicidal drug overdose permit the following conclusions:

Part II. The concomitant ingestion of ethanol with drugs in suicidal overdose is a common occurrence but does not appear to present a common problem:

(a) The incidence of ethanol ingestion in patients with severe overdose is one-half that in mild overdose.
(b) Of patients in coma the time until they are responsive is three times shorter in those who have taken ethanol compared to those who have not.
(c) Patients who have, in contrast to those who have not, taken ethanol with their overdose usually have exogenous depression, have had psychiatric care less frequently and have taken psychotropic drugs less frequently.

(d) Ethanol does not affect the pharmacokinetic disposition of amobarbital but does increase the area under the curve and decrease the beta half-life of diazepam.
(e) The pharmacokinetic elimination of ethanol is not a rate limited process. It's elimination is described by dose-dependent Michaelis-Menton kinetics.
(f) The pharmacokinetic elimination of amobarbital appears to approach a zero order process with increasing dose of drug.

Part III. The recommendation for the routine use of gastric instillation of activated charcoal after drug overdose is not supported when applied to the actual problem.

(a) Activated charcoal administered on arrival at hospital did not decrease the chance of a patient having a severe enough overdose state to warrant admission.
(b) Of patients in coma the prior administration of activated charcoal did not decrease their duration of coma.
(c) Activated charcoal did not seem to decrease the absorption or increase the elimination of salicylate.

3. Significance of Project

The data from the project to date has been enlightening in 2 major aspects. First, the common belief that ethanol enhances the severity of suicidal overdose appears incorrect because the group of patients who ingest ethanol with their drugs probably ingest less drug. Second, the common recommendation for routine use of activated charcoal in drug overdose is not substantiated in this first controlled drug overdose study in man. The very short duration of coma in our experience could be secondary to aggressive care of vital functions, in particular, hemodynamics and especially liver blood flow. Studies of the influence of liver blood flow on the clearance of common drugs are in progress.

4. Findings Relevant to Reducing Problems Associated with Non-Medical Drug Use

Our findings to date shed new light on our understanding of the very common social problem of drug abuse in suicidal overdose. Those patients who do ingest ethanol with their drugs are a distinct group and the interaction between ethanol and the drug does not appear to have clinical significance. Our findings also seem to settle the question of usefulness of activated charcoal in the extremely common problem of pediatric accidental or adult suicidal drug overdose. This form of almost standard treatment appears unwarranted and in fact may delay the more important aspect of treatment namely aggressive maintenance of vital functions. We do not see any immediate answer to the problem of patients demanding and physicians liberally prescribing drugs. There is definitely an inverse relationship between the affluence of our society and our tolerance to minor discomforts. We suggest that aggressive advertising to the public and physician plays a large role.

5. Future Directions of Research Projects

We believe that advances in the treatment of accidental and suicidal drug overdose lay in two areas. First it is known that most drugs are "eliminated" from the body by hepatic degradation. It has been shown that the clearance of some drugs is very dependent on liver blood flow. The importance of liver blood flow on the clearance of drugs commonly used in drug overdose has not been studied. Liver blood flow may be reduced in overdose states and should be able to be increased to normal or greater than normal. This is one of the few physiologic factors which can be manipulated since hepatic enzyme induction is not practical as a means of enhancing drug elimination. It is time we applied the same approach in manipulating hepatic physiology as we have with enhancing renal clearance of drugs. We also plan studies with 2 commercial hemoperfusion devices available for clinical investigation. These consist of pumping blood directly over an activated charcoal matrix. Early studies in humans have shown them to be safe and very efficient. Further studies with charcoal hemoperfusion are required in patients in severe coma from different drugs. This non-specific treatment method could prove useful in the management of severe overdose in children and adults.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
J.E. Tong J. Tong	Psychology
INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE	
University of Guelph, Guelph, Ontario	
PROJECT TITLE – TITRE DU PROJET	
Effects of ethanol and tobacco on human performance and physiological variables.	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES / TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-1977	$27,000 / 824-4120

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☒ BIOMEDICAL BIOMÉDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

In different experiments ethanol and tobacco are administered separately and jointly to normal male subjects who are habitual cigarette smokers. The dependent variables being examined are the electro-dermal orienting response, heart-rate, heart-rate variability, velocity judgment and scores from an auditory vigilance task. Comparisons are also made between smokers and non-smokers for the effects of ethanol on the above variables. Survey data concerned with the relationship of smoking and drinking have been obtained and pilot data for the effects of different dosage levels of ethanol on tobacco consumption.

Up to a blood alcohol concentration of 0.08% ethanol and tobacco summate to produce a significant increase in heart-rate of about 12-20 beats per minute, but at the 0.1% BAC level a third of the subjects show a deceleration in heart-rate irrespective of the usage of tobacco. With auditory vigilance non-smokers consistently detected more signals throughout the 60 minute test. A significant interaction showed that while non-smokers detected fewer signals as the test progressed, smokers having smoked before testing increased their number of detections. Extraverted non-smokers gave significantly higher scores than introverted non-smokers with the converse being present for smokers. Survey data indicates that smokers report different subjective effects for ethanol than non-smokers, these mainly being increased arousal for the former and a sedative effect for the latter. Observational data indicate a linear relationship between the puff rate per cigarette (nicotine intake) and blood alcohol concentration.

The results suggest that tobacco and alcohol abuse should be regarded as a unitary problem and that corrective measures aimed at the prevention of tobacco smoking in the young age groups will also reduce the incidence of alcohol related problems.

Future research will examine the interaction of tobacco and ethanol on behavioral variables.

Publication

J.E. Tong, G. Leigh, J. Campbell and D. Smith. "Tobacco smoking, personality and sex factors in auditory vigilance performance. British Journal of Psychology, 1977. (To appear)

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Noe ZAMEL, M.D. Noe Zamel	Trihospital Respiratory Service, Dept. of Medicine.

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Toronto (Address: Mount Sinai Hospital, Toronto, Ontario M5G 1X5

PROJECT TITLE – TITRE DU PROJET Reversibility of Pulmonary Function Abnormalities in Cigarette Smokers After Cessation of Smoking.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-1977	$75,000	(416) 596.4473

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[X] BIOMEDICAL – BIOMÉDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[ ] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

The objective of the project is to determine which tests of lung mechanics can be improved and if carbon monoxide lung diffusion can increase after cessation of smoking in apparently normal individuals with MM and MZ alpha-1-antitrypsin phenotype. The method of approach is to obtain extensive measurements of lung mechanics and single breath lung diffusion capacity for carbon monoxide in regular cigarette smokers with MM and MZ phenotypes. The tests are repeated after eight weeks of smoking abstention.

Preliminary results are available in 21 smokers who successfully stopped smoking and are of the MM phenotype. There was no significant change in carbon monoxide lung diffusion but some of the lung mechanics tests (maximum expiratory flows breathing a mixture of helium + oxygen; slope of phase III; and frequency dependence of dynamic lung compliance) showed improvement. An original observation was that lung elastic recoil pressures decreased after cessation of smoking by a small amount but which was statistically significant. This was interpreted as due to a reversibility of alveolar duct inflammation and/or muscular constriction.

The significance of the project is to establish which aspects of pulmonary functions may be reversible and if individuals with MZ phenotype have the same improvement as the general population (MM phenotype) following cessation of smoking.

The preliminary findings are encouraging in showing several aspects of lung function that can recover after smoking abstention.

This project will now be directed to the second phase which is to obtain data in MZ phenotypes.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
RONALD E. CUTLER	NON-MEDICAL USE OF DRUGS DIRECTORATE

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

WATER STREET RESEARCH GROUP, #205 - 310 Water Street, Vancouver, B.C. V6B 1B6

PROJECT TITLE - TITRE DU PROJET

An Ecological Perspective of the Vancouver Treatment System: Impact of a New

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE Agency 681-9714

FIELD OF RESEARCH SUJET DE LA RECHERCHE									
	X	EVALUATION ÉVALUATION		BIOMEDICAL BIOMEDICALE		BEHAVIORAL COMPORTEMENT	X	SOCIAL SCIENCE SCIENCES SOCIALES	MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

This study, currently in the data collection stage, was derived from a first attempt, on the part of the Program Implementation Bureau of NMUD, to transplant treatment programs which have been successfully developed in one region (Alternatives, Montreal) to other regions (Alternatives, Vancouver).

In general the study has attempted to assess the extent to which various impacts - intended or unintended, primary or secondary - result from interactions between the Alternatives program and those agencies which make up the Vancouver treatment system, other related organizations and the community at large. Changes within the Alternatives program, as it is conducted in both Vancouver and Montreal, and changes within the Vancouver treatment system are being assessed at several points in time corresponding to four implementation stages beginning at the point where the decision to transplant was taken and ending at a point six months after the termination of NMUD funding for Alternatives.

As a secondary objective the treatment system in Vancouver is being examined with a view to the identification of a number of subdivisions within the system and the organizational environment in which the system operates.

The methods employed are both qualitative and quantative and include repeated interviews among various samples, observations, data obtained from documentary sources, agency referral data, various client and volunteer characteristic data and reports of contacts between representatives of Alternatives and other agencies.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DÉPARTEMENT
Park O. Davidson, Lynn Alden	Psychology

INSTITUTION AND ADDRESS - ÉTABLISSEMENT ET ADRESSE
University of British Columbia, Vancouver, B.C. V6T 1W5

PROJECT TITLE - TITRE DU PROJET
Drug and alcohol treatment program development - B.C./Yukon

YEARS FUNDED - ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED - SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER - NUMÉRO DE TÉLÉPHONE
1976/77	$63,715.75	(604) 228-6327

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[X] EVALUATION ÉVALUATION
[ ] BIOMEDICAL BIOMEDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

This project was the first phase (one year) of a four-year project to establish a treatment development team for drug and alcohol programs in British Columbia and the Yukon. The major goals of this team are to assist selected treatment agencies in establishing a program monitoring and evaluation system to improve the quality of their treatment effectiveness; to help selected programs in the systematic development of new and innovative treatment programs; to develop methodology which can be used by other programs for evaluating their operations; and to provide a research milieu for training graduate psychology students in program development and evaluation skills for the alcohol and drug treatment fields. Phase I was largely devoted to gaining entry to existing agencies, setting up and testing data collecting instruments, and designing innovative programs. Diagnostic reports have been completed on seven agencies in British Columbia and two in the Yukon. A life-style change prevention program for heavy drinkers has been designed and is operating within the Burrard Health Unit of the City of Vancouver. The approach is through behaviour control techniques involving the drinker before his network of social supports has been destroyed. Evaluation of this self-management controlled drinking program is currently under way.

Outcome data on one alcohol program in the Yukon have been collected for almost a year, and the team is cooperating with the Alcohol and Drug Services Division of the Yukon Territorial Government in setting up and evaluating regional community services to small centres. The approach taken is that of multiple treatment options coordinated by Native community workers.

In all of the agencies with which the team has worked the major thrust has been the development of instruments which monitor client outcome, and the collection of data relating to client, treatment, and agency characteristics. The long-range goal of the second phase of this project will be to identify those factors

within agencies which influence successful client outcome.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DÉPARTEMENT
Robert W. Hetherington	Psychiatry

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

University of Saskatchewan, Saskatoon, Sask.

PROJECT TITLE – TITRE DU PROJET

Saskatoon Native Followup Society: Program Evaluation Project

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1977-78	$27,016.00	343-2041

FIELD OF RESEARCH SUJET DE LA RECHERCHE

[x] EVALUATION ÉVALUATION [ ] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The Saskatoon Native Followup Society: Program Evaluation Project is presently in the planning stages. Implementation of the proposed project is contingent on ministerial approval of funding.

The purpose of this twelve-month evaluation project is to assess the impact on behaviors and attitudes of natives served by the Saskatoon Native Followup Society program. Under the funding from the Non-Medical Use of Drugs Directorate, a major emphasis of the program is placed on providing assistance to native people who have problems arising from alcohol or drug abuse. The Followup program concentrates not only upon the removal of the abusive behavior but also attempts to deal with the social circumstances surrounding alcohol or drug abuse.

We propose to apply a quasi-experimental design in the evaluation of this program, involving measurements on outcome variables before and after contact with the Followup Program, and comparison with a control group where Followup services are not available. The outcome measures will examine changes over time in drinking behavior, vocational adjustment, social involvement, self-sufficiency and self-concept.

Information is to be gathered primarily from interviews with a sample of 50 natives from the Followup program, and 50 natives from the control group drawn from a Native Alcohol Center in another region. These interviews will be conducted by native interviewers. Data will also be collected from records of the Followup Program workers, interviews with officials from native and non-native agencies whose services are used by those in the sample, and from official records where possible.

Evaluation of the Native Followup Society will provide scientific information on how well the program is meeting its objectives. In addition, our work with the Society will set up a system for collection of information in the future such that program personnel themselves will be able to monitor their activities and level of success.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. Stephen L. Milstein	INRS - Santé
INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE: Hôpital St. Jean-de-Dieu, Rue Hochelaga, Montréal, Québec	
PROJECT TITLE TITRE DU PROJET: Traitement de l'abus des drogues: recherche et développment	
YEARS FUNDED ANNÉES SUBVENTIONNÉES: 1974 - 1979	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES: $376,537.18
TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE: 256-9004	

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [X] EVALUATION ÉVALUATION [ ] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Traitement de l'abus des drogues

Recherche et développement

Le projet "Traitement de l'Abus des Drogues: Recherche et Développement" est subventionné par le Bureau de l'Usage Non-Médical des Drugues et intégré à l'INRS-Santé. Il est sous la responsabilité du Dr. S. Milstein et du Dr. C. Mercier-Tremblay. Il vise 1) à développer une méthodologie d'évaluation formative basée sur les principes de la recherche-action: 2) à appliquer cette méthodologie auprès d'agences de traitement de l'alcoolisme et autres toxicomanies: 3) à fournir des données de recherche aux programmes-participants de façon à leur permettre d'améliorer leur intervention.

La recherche se déploie suivant trois volets, description de la clientèle, du processus de traitement et des effets de l'intervention. Ceci de façon à apporter des éléments de réponse à la question générale "quel type de traitement répond mieux à quel type de clientèle" ou encore "les résultats de traitement X,Y,Z observés peuvent se rattacher à quel type de clientèle ou à quel processus d'intervention".

Le projet de 4 ans, est en opération depuis 2 ans. L'équipe de chercheurs travaille en collaboration avec 7 agences de traitement. Le projet est opérationnel aux niveaux de la description de la clientèle et des effets du traitement (données de base et follow-up). L'élaboration des procédures de description du traitement est en cours.

Pour répondre à ses objectifs d'évaluation formative, l'équipe de recherche travaille en collaboration étroite avec les agences de traitement participants. Ce qui se manifeste à deux niveaux: les problématiques de recherche sont toujours définies à partir des problèmes et des questions posés par les agences; lorsque c'est nécessaire, des instruments de recherche "sur mesure" sont développés. Ainsi, les domaines et les critères d'évaluation des effets du traitement auprès du client on été établis à partir des objectifs de traitement des agences et des instruments "ad hoc" ont été conçus pour ce faire.

D'autre part, les résultats sont transmis aux agences, dès qu'ils sont disponibles. A titre d'exemple des agences ont reçu des compte-rendu de leur clientèle masculine et féminine et de son évolution dans le temps, de même qu'une description de l'atmospnère de leur programme établie à partir de perceptions du personnel et des clients.

Les efforts du projet porteront dans les prochains mois sur la description du milieu de traitement et l'analyse des données d'évaluation.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
David P. Nowlis, Ph.D.	Psychiatry

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Institute of Community & Family Psychiatry, Jewish General Hospital, Montreal

PROJECT TITLE TITRE DU PROJET Training in voluntary self-governance for patients with self-governance disorders: effects on drug use

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1975-76, 1976-77	24,225.00	514 341-6211

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[X] EVALUATION ÉVALUATION
[ ] BIOMEDICAL BIOMEDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

TRAINING IN VOLUNTARY SELF-GOVERNANCE FOR PATIENTS WITH SELF-GOVERNANCE DISORDERS: EFFECTS ON DRUG USE

1. PROJECT DESCRIPTION - Fifty-four subjects with drug use problems associated with psychomatic symptoms were chosen on a first-come, first-served basis from a large number of volunteers and referrals. Eighteen had self-regulation problems involving headache and drug-use; 18 had self-regulation problems involving insomnia and drug-use; and 18 had self-regulation problems involving hypertension and drug use.

All Ss were checked by their own physician, then given the Cattell 16 PF Test, the Rotter I-E Scale, and a medical history interview including a drug use section designed by Blum and associates. Six subjects in each symptom category were then randomly assigned to biofeedback treatment (15 to 20 hour sessions over 2 months); six to verbal relaxation training (15 to 20 hour sessions over 2 months), and six to a control group observed for two months with no treatment. The control group was then given a combination of biofeedback and relaxation treatment over two months.

2. RESULTS - Overall within subject change in drug use from pre-training to post-training was significant by both measures used. On the average before training subjects took a mean of 2.2 kinds of drugs per week, in addition to alcohol and tobacco use (the data on which have not yet been analyzed), resulting in an average for all subjects of 22.2 various sorts of pills per week. After training, kinds of pills were reduced to an average of 1.7 per week (correlated t value = 4.1, $p < .001$), with a concommitant decrease to a total of 17.5 pills per week (correlated t value = 3.9, $p < .001$). These changes were maintained remarkably well in the year after follow up. Data obtained with 52 of the original 54 Ss showed year later pill use at 17.8 pills per week and kinds of pills still at 1.7 per week.

Other tests performed on the data of subjects with different symptoms revealed evidence of training-induced decrease in number of kinds of drugs for the three types of treatment for insomniacs and similarly for the subjects with headaches, but not for subjects with hypertension. Similarly, there was mild but significant evidence for improvement in some symptoms for insomniacs and subjects with headaches, but not for those with hypertension. For headaches, number per week was especially reduced, and average intensity was somewhat reduced, but average length of headache was not changed at all. For insomnia, average time to sleep onset was especially reduced. Decreases in drug use were maintained well at the time of the year later follow up in both the insomnia and in the headache groups.

...2

The following 16 PF personality variables were correlated with a pre-post reduction in use of kinds of medication for the whole group (N=54): tense ($p < .001$), conscientious ($p < .01$) and anxious ($p < .04$). In addition, subjects manifesting a tendency towards an internal locus of control on the Rotter I-E Scale showed a tendency ($p < .06$) to decrease types of medication in post training measurements.

3. SIGNIFICANCE - We feel our most significant findings are: 1) the excellent maintainance of improvement after one year, indicating the need for better understanding of self-sustaining mechanisms in self-governance methods of relazation; 2) the fact that verbal relaxation methods were as effective as biofeedback methods in reducing drug use and symptomatology, indicating the possibility of programs made much less expensive through lowering equipment costs; and 3) the fact that the subjects who responded the best were those with high anxiety who also had already developed some sense of internal control, indicating the possibility of development of theory and screening techniques for heightening the probability of success with such methods. None of these findings had been predicted in advance.

4. RELEVANCE TO NON-MEDICAL DRUG-USE - On the one hand, our findings have some practical significance, because they may show the road toward inexpensive, easy-to-teach self-governance methods which effectively reduce drug use in anxious people prone to headache or insomnia. On the other hand, our findings also have some theoretical significance, in contributing to a better understanding of the interrelationship of self-care techniques and drug-use tendencies in the same person.

5. FUTURE DIRECTIONS - Urine samples were regularly collected from all Ss, without revealing the reason. These samples are now being analyzed, and the final data will be ready in a month. Results will be intercorrelated with all other variables, as they provide objective evidence pertaining to drug use tendencies.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER - NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT - DÉPARTEMENT
G.W. Piper	Social & Preventive Medicine

INSTITUTION AND ADDRESS - ÉTABLISSEMENT ET ADRESSE
University of Saskatchewan, Saskatoon

PROJECT TITLE - TITRE DU PROJET
Evaluation of Early School Education in Smoking & Health

YEARS FUNDED - ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED - SUBVENTIONS ASSIGNEES	TELEPHONE NUMBER - NUMÉRO DE TÉLÉPHONE
15 months	$9,000.00	306-244-0191

FIELD OF RESEARCH - SUJET DE LA RECHERCHE

- [x] EVALUATION - ÉVALUATION
- [ ] BIOMEDICAL - BIOMEDICALE
- [ ] BEHAVIORAL - COMPORTEMENT
- [ ] SOCIAL SCIENCE - SCIENCES SOCIALES
- [ ] MULTI-DISCIPLINARY - MULTI-DISCIPLINAIRE

Previous research by the investigator has shown that children's knowledge and attitudes about smoking and health change very little between grades seven and twelve. This is the period when recruitment to smoking is greatest. It seems that children who are well-informed about the health hazards of smoking and who consider those hazards personally relevant are less likely to take up smoking than others who do not have that knowledge and attitude. This suggests that success in education about smoking may require the inculcation of appropriate knowledge and attitudes before grade seven.

A curriculum guide has been prepared and introduced to teachers of children in kindergarten and grades 1 through 3 in selected "pilot" schools in and around Moose Jaw, Sask. The guide was first introduced in January 1976 and revised in the summer of 1976. Resource materials and persons have been made available. A similar group of schools has been selected as controls. No special program has been introduced into control schools.

Effectiveness of the program will be judged in the long run against the smoking habits of exposed children when they reach grade 5.

In the short run, during May-June 1977 measurements will be made of the type and quantity of educational exposure in both pilot and control schools.

100 children from pilot schools and 100 children from control schools will be interviewed to determine their knowledge and attitudes about material presented in the curriculum guide.

Baseline data on the smoking habits of grade 5 students in June 1976 showed 57.7% girls and 71.9% boys claim they have never smoked. There was no significant difference in this regard between pilot and control schools but significantly more children from the City of Moose Jaw had never smoked than for children from rural areas (Boys 54.4% vs. 30.5%; Girls 68.0% vs. 52.4%).

Assessment of the school program will be conducted by Dr. S.J. Thiessen, College of Education, University of Saskatchewan.

21 April 1977

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. Angus E. Reid	Social and Preventive Medicine

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Faculty of Medicine, University of Manitoba, 753 McDermott Avenue, Winnipeg, Manitoba.

PROJECT TITLE TITRE DU PROJET
A STUDY OF THE IMPACT OF RESEARCH ON ALCOHOL AND DRUG TREATMENT PROGRAMS IN CANADA

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-1978	$182,853.00	786-4321

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[X] EVALUATION ÉVALUATION
[ ] BIOMEDICAL BIOMÉDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

REDRAFT OF THE KNOWLEDGE OF SOCIAL ACTION: A STUDY OF THE IMPACT OF RESEARCH ON ALCOHOL AND DRUG TREATMENT PROGRAMS IN CANADA

This study examines three issues relevant to policy with respect to alconolism and drug treatment in Canada:

a) What is the impact of program oriented research on the development of treatment programs and what are the processes and mechanisms by which research results are translated into policy?

b) What modalities of treatment are currently being utilized in Canada's treatment system and how do these relate both to current knowledge and the efficacy of treatment approaches and to information on the incidence and prevalence of alcoholism and drug dependency in Canada?

c) How have the initiations of both the provincial and federal governments over the past decade acted to give shape to the treatment systems which currently exist in the provinces and to what extent do they explain the variations across these provinces?

In order to provide answers to these questions, a national study of specialized alcoholism and drug treatment centres was conducted in the summer and fall of 1976. Extensive information on over 400 treatment agencies were collected through interviews with agency directors and staff. A by-product of this research - a comprehensive national directory of specialized alcohol and drug treatment agencies - was prepared in draft form in November of 1976 and a revised final version was forwarded to the Non-Medical Use of Drugs in May of 1977.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Schlegel, R. P. Ronald P. Schlegel	Kinesiology
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of Waterloo, Waterloo, Ontario	

PROJECT TITLE TITRE DU PROJET The effects of factual, value-oriented and decision-making alternative exposures on alcohol attitudes and behaviour under changing social situations: Evaluation of an educational program

YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1976-78	$33,674.66	885-1211 ext 3089

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[X] EVALUATION ÉVALUATION
[ ] BIOMEDICAL BIOMEDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The present evaluation research, which is currently in progress, has developed three alcohol education programs and is examining their relative effects on knowledge, attitudes, intentions, behaviour and abusive drinking for a sample of grade 8 boys and girls. The three programs include: (a) facts only, where the primary focus is on a factual history and explanation of alcohol and its chemical effects; (b) facts plus values clarification, where all of the material for the facts group plus selected values clarification procedures are presented; and (c) facts plus values clarification plus decision-making, where, in addition to (a) and (b), there exists a decision-making phase. In the latter group, students will complete a decisional balance sheet to determine for themselves gains and losses for alcohol use vs a competing, alternative behaviour instrumental to similar values. The resulting decision is then shared with another student who has made a similar decision, and together with this "buddy" the anticipated difficulties for adhering to this decision are reviewed. Finally, a self-contract pertaining to the next 6 months is written and sealed. A control group is also included in order to compare the effects of the experimental groups against baseline measures. Six months after the delivery of the above programs and just prior to students' graduation from elementary school to high school, half of the students in each group will be randomly assigned to a re-exposure condition where a summary exposure to their respective educational treatment will be given. The intent of the re-exposure is to relate the content studies in the grade 8 program to the anticipated experiences of high school.

The dependent measures are being obtained immediately after the educational exposure (November, 1976); 6 months later (May, 1977); and 12 months later (November, 1977). The last repeated measure will enable an assessment of the persistence of the educational effects when students change social environment. (i.e., graduate to high school). The data collection has been completely separated from the program delivery using several strategies in order to minimize certain demand effects. (No findings can be summarized at this point in time since initial data are presently being keypunched, processed onto computer tape, etc.).

The significance of the research pertains especially to its emphasis on primary prevention in two respects: (a) The onset of initial drinking will be delayed, or perhaps entirely prevented. This is important since problem drinking is more likely to occur for persons starting to drink earlier in life. (b) The educational process will attempt to prevent abusive drinking among those who have already experimented with alcohol.

A major benefit of the research is that the effects of the alcohol education methods are being evaluated using a rigorous methodology. The method determined most effective by this study can subsequently be employed in school systems across Canada. Also, process measures incorporated into the study will permit some analysis of the dynamics underlying differences in results among the treatment groups. The ultimate benefit of this understanding will be to implement effective programs to reduce the incidence of alcohol-related problems in our adolescent population.

Future directions for this research will be to conduct longer term follow-ups as well as to assess the effects of repeated exposures to alcohol education.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
H.C.Fibiger and M.E.Corcoran	of Psychiatry, Division of Neurological Sciences

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

University of British Columbia, Vancouver, B. C. V6T 1W5

PROJECT TITLE – TITRE DU PROJET

Neurochemical substrates of drug-reinforced behaviour

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1976-1977	$25,000	(604)-228-2984, 228-2015

FIELD OF RESEARCH SUJET DE LA RECHERCHE

[ ] EVALUATION ÉVALUATION	[ ] BIOMEDICAL BIOMÉDICALE	[ ] BEHAVIORAL COMPORTEMENT	[ ] SOCIAL SCIENCE SCIENCES SOCIALES	[X] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Humans self-administer a wide variety of drugs, but the factors underlying the initiation and maintenance of this behavior remain obscure. It is likely, however, that at least part of the motivation for drug self-administration lies in the direct pharmacological reinforcing properties of the drugs themselves. Support for this view comes from the observation that many drugs abused by humans are also self-administered by animals. Previous studies suggest that self-administration of psychomotor stimulants may depend on the availability of central catecholamines (noradrenaline and dopamine); this is suggested by the finding that self-administration is reduced or abolished by pretreatment with drugs that block the synthesis or postsynaptic effects of catecholamines. These data led us to propose that psychomotor stimulants are self-administered because they facilitate the synaptic activity of central catecholaminergic pathways, leading to the straightforward prediction that selective and specific lesions of these pathways with 6-hydroxydopamine (6-OHDA) should block self-administration of drugs. Our project is designed to test the prediction.

We have begun by examining the effects of 6-OHDA-induced lesions upon the intravenous self-injection of cocaine by male rats. The dosage of cocaine available was 0.75 mg/kg/injection, and the lesions were made after the rats had established a stable baseline of self-injection. Lesions of the noradrenergic pathways of the brain had no effect upon self-injection of cocaine, whereas self-injection was suppressed after lesions of the dopaminergic nucleus accumbens. Self-injection of apomorphine, a psychomotor stimulant that stimulates postsynaptic receptors for dopamine, was unaffected by lesions of the accumbens, indicating that the disruption of cocaine self-injection produced by these lesions was not a function of motor deficits. We tentatively concluded that 6-OHDA-induced lesions of the nucleus accumbens disrupt the positive-reinforcing properties of cocaine, and we are currently performing further experiments to test this hypothesis and to examine the effects of similar lesions upon the self-injection of other drugs, such as morphine.

It is hoped that these experiments will enable us to identify the location and nature of the neural pathways whose activity mediates the reinforcing effects of various drugs of abuse. In addition to their obvious theoretical interest, these experiments may result in the stimulation of specific pharmacological strategies for dealing with drug abuse in humans.

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR
W.F. Forbes

DEPARTMENT – DÉPARTEMENT
Statistics

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Waterloo, Waterloo, Ontario, N2L 3G1

PROJECT TITLE – TITRE DU PROJET
The Waterloo Smoking and Health Project

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TELEPHONE
1967-1977	$1,072,500.	(519)885-1211, ext. 3473

FIELD OF RESEARCH SUJET DE LA RECHERCHE

EVALUATION ÉVALUATION	BIOMEDICAL BIOMEDICALE	BEHAVIORAL COMPORTEMENT	SOCIAL SCIENCE SCIENCES SOCIALES	MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE
				X

This research program consists of a number of inter-related projects, designed to reduce the undesirable consequences of tobacco use in Canada.

The first project involves the on-going analysis to tar, nicotine, and carbon monoxide levels of currently-available and newly-released cigarettes in Canada. Since this aspect of the project has been supported since 1968, sufficient data have been accumulated to permit a meaningful study of secular trends in the tar and nicotine deliveries of Canadian cigarettes. Further, this information, in conjunction with results from studies of carbon monoxide and other gas deliveries, will be used to develop an index which estimates the degree of hazard of a cigarette. The purpose of the second project is to obtain more reliable estimates of cigarette smokers' exposure to toxic smoke constituents. The third project deals with three types of surveys. First, a survey of the smoking habits of Canadian school children' secondly, a similar survey involving a Kitchener-Waterloo adult population and, thirdly, a survey designed to estimate the average length of cigarette butts discarded by various groups identifiable within the Canadian smoking population. The fourth project concerns the analyses and presentation of data related to smoking and health studies. This project includes a study of smoking and other risk factors as they affect mortality from various diseases, a study of econometric models designed to assess the role of price and advertising in cigarette consumption, and analyses of the data arising from the surveys which comprise the third project. The fifth project involves the estimation of cadmium and lead levels in various tissues obtained at autopsy from smokers and non-smokers. The aim is to investigate the hypothesis that tissue levels of cadmium and lead alter the cause-of-death pattern in a group of exposed individuals, and also to estimate the extent to which cigarette smoking contributes to the human body burdens of these trace metals.

The key findings of the first project are reported in the publication of the reports on tar and nicotine deliveries of Canadian cigarettes. With respect to the second project, an analysis of the smoking habits of individual smokers suggests that smokers can be subdivided into groups depending on their smoking habits. The key findings on the third project are listed in the publication of a survey of the smoking habits of Canadian school children and by the monitoring of butt lengths in different Canadian populations. Also, an estimate of price elasticities for Canadian cigarette consumption has been obtained (project 4), and cadmium and lead levels in various tissues obtained at autopsy from smokers and non-smokers have been estimated (project 5).

The significance and relevance of the first project is related to the area of reducing the risk to smokers, because quantitative knowledge of smoke constituents is a prerequisite for progress in this area. The second project aims to reduce risks to smokers since, if preliminary results are confirmed, the data suggest that the major proportion of the smoking population is able to adjust satisfactorily to a less hazardous cigarette on a long term basis. Further work on this project aims to estimate the size of the group of individuals who are able to adjust their smoking habits in this way. Concerning the third project, these studies aim to monitor cigarette consumptions for various parts of the Canadian population, particularly in school children. The fourth project is relevant to the problem area of starting to

smoke, cessation of smoking and reducing risk to smokers. Both the results on the econometric models and those from the risk factor analyses should provide applicable knowledge in the three NMUD problem areas mentioned. The fifth project addresses itself to the areas of reducing risk to smokers in that lead and cadmium, which are known to be present in tobacco smoke, may be responsible for part of the excess mortality and morbidity associated with the use of tobacco. Specific results which it is aimed to achieve are the establishment and analysis of a data base which will indicate the role of lead and cadmium in tobacco smoke, in the adverse health consequences of tobacco use.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
H.M. Simpson	

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

Traffic Injury Research Foundation of Canada, 1765 St.Laurent Blvd., Ottawa K1G 3V4

PROJECT TITLE – TITRE DU PROJET

Incidence of Alcohol in Fatally Injured Drivers and Pedestrians for 1974-1975.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1		

FIELD OF RESEARCH – SUJET DE LA RECHERCHE

EVALUATION – ÉVALUATION	BIOMEDICAL – BIOMÉDICALE	BEHAVIORAL – COMPORTEMENT	SOCIAL SCIENCE – SCIENCES SOCIALES	MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE
☐	☐	☐	☐	☒

This project was designed to (1) obtain data on drivers and pedestrians fatally injured in motor vehicle accidents during 1974 and 1975 from as many provincial coroners/medical examiners as feasible; (2) provide statistical information on these fatalities with special reference to the epidemiology of alcohol; (3) provide annual comparisons using data already on file for 1973 fatalities; (4) compute risk factors using fatality data for 1974 and comparable population-at-risk data from a 1974 roadside survey.

A minimum of ten variables were abstracted on each victim from provincial records in eight of the ten provinces yielding a total of 4,581 drivers and 2,692 pedestrians.

Motor vehicle fatalities declined by approximately 3% from 1974 to 1975 with the decrease occurring in each victim category, namely, drivers, passengers and pedestrians. Drivers accounted for approximately 50% of all victims during 1974 and 1975 with passengers and pedestrians accounting for 29% and 20%, respectively. Automobile drivers accounted for 67% of all fatally injured drivers. Among the 2,839 fatally injured automobile drivers, 2,249 (79%) were tested for blood alcohol content (B.A.C.) and at least 1,084 (38%) were impaired (B.A.C.$\geq$.08%). Since the decision to perform a B.A.C. test is contingent on death time, fatalities were dichotomized in terms of that variable. Of the 2,839 automobile driver fatalities, 2,462 (87%) died within the first six hours of crash. Among this group of drivers, 88% were tested for B.A.C. and 43% were impaired.

The magnitude of the impaired-driver phenomonon appeared to remain stable from 1973 to 1975. Among all fatally injured automobile drivers in 1973, at least 39% were impaired, at least 38% were impaired in 1974 and at least 39% were impaired in 1975. The phrase "at least" is used to indicate that the method of estimating percent impaired is conservative based on the assumption that all non-tested drivers had B.A.C.'s equal to zero. Using aggregates based on death-time less-than-six-hours, a similar stability in percent impaired over the years was observed, with 44%, 43% and 43% in the years 1973, 1974 and 1975 respectively.

A small sample of tractor trailer operators were available for study. Among this group of 71 fatally injured drivers, at least 14% had been drinking and at least 7% were impaired.

Among fatally injured motorcycle operators, at least 30% were impaired. More interesting, however, was the finding that at least 12% of motorcycle fatals had positive B.A.C.'s of less than .08%. This frequency of low B.A.C.'s is higher among motorcycle fatalities than among any other major group of fatally injured drivers suggesting that, perhaps, the current legal limit (.08%) is too liberal as it applies to motorcycle operators.

Of all motor vehicle operators, fatally injured snowmobile drivers were the most frequently impaired. During 1974 and 1975 at least 58% had been drinking and at least 47% were impaired. Of the snowmobile drivers who died within six hours of crash, at least 67% had been drinking and at least 54% were impaired.

A review of the risk factors methodology revealed that the majority of limitations common to the risk factors approach exist as a function of the questionable generalizability of the roadside survey data and not that of the fatality data. Risk factor derivations were replicated from previous work utilizing a matching technique which more adequately approximated the roadside survey parameters and reduced the magnitude of the conservative bias explicit in the initial risk factors formulation. This procedure resulted in a substantial increase in the absolute magnitude of the total impairment risk factors, but the relative magnitude of the risk factors remained substantially unaltered.

The assignment of an objective impairment criterion such as .08 to the study of fatally injured pedestrians is necessarily spurious and misleading. Nevertheless, such a criterion provides a frame of reference for comparison with other groups of fatally injured persons. Among pedestrian fatalities aged 14-64, at least 47% had been drinking and at least 39% had B.A.C.'s in excess of .08. The lowest frequency of impairment among pedestrians aged 16-64 is found among those fatalities aged 25-34. This finding stands in marked contrast to the data of fatally injured drivers, among whom the 25-34 age group had the highest frequency of impairment. The B.A.C.'s of fatally injured pedestrians tends to be substantially higher than the B.A.C.'s of driver fatalities. Fifty percent of fatally injured pedestrians who had been drinking had B.A.C.'s in excess of .20 mg.%; 16% had B.A.C.'s in excess of .30 mg.%.

At one level the data show that despite the apparent massive increases in countermeasures and intervention programmes aimed at impaired driving, the effects have been nominal. However, the major limiting factor in that respect is the adequacy of a reliable data base from which to make such statements. The prime purpose of this particular epidemiological research has been to establish a comprehensive national data base with adequate parameters from which statements regarding the magnitude of the problem and its characteristics can be made. Indeed, future countermeasures are likely to be highly ineffecient if, in fact, the characteristics of the problem, attributes of the relevant target groups and the like have not been previously defined. In this respect future research at the Traffic Injury Research Foundation of Canada is designed primarily toward the establishment of a national data base with respect to traffic fatalities, which will permit adequate problem definition, the inevitable description of high-risk groups and the explication of the factors or variables that render those groups at high risk.

Publications

Simpson, H.M. Warren, R., and Pagé-Valin, L. Analysis of fatal traffic crashes in Canada, 1974-1975: Focus the impaired driver. T.I.R.F. Reports, February 1977.

Simpson, H.M. Impaired Driving. Canadian Medical Association Journal, 1977, 116, 121-122.

Warren, R.A. Empirical evaluation of impaired driver legislation. Paper presented at the 13th Annual Meetings of the Traffic Injury Research Foundation of Canada, Ottawa, October 1976.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER -- NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT - DÉPARTEMENT
M. Gent, L. Gerson L Gerson	Clinical Epidemiology and Biostatistics
INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE	
McMaster University, 1200 Main Street West, Hamilton, Ontario L8S 4J9	

PROJECT TITLE - TITRE DU PROJET

Epidemiologic Field Station for Drug Related Problems

YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1975-1977	180,000	525-9140 ext. 2791

FIELD OF RESEARCH SUJET DE LA RECHERCHE

☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☐ BEHAVIORAL COMPORTEMENT ☒ SOCIAL SCIENCE SCIENCES SOCIALES Epidemiology ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

A monitoring system has been developed which is designed to answer the questions: 1) what proportion of specific health and social problems may be attributed to drugs? and 2) what are the characteristics of the group(s) which are at greatest risk for drug involvement? The focus of the system concerns alcohol involvement in the following problems: various types of aggressive behaviour, impaired driving, teenage drinking and long term heavy use.

Surveillance of the above events is accomplished through the use of routinely collected records obtained from a number of cooperating agencies and organizations, these include: the police department, fire marshall, hospitals, traffic department, social service agencies and the liquor board.

The results presented in the first report of the Epidemiologic Field Station showed Alcohol was implicated in 28.8% of all acts of aggression but over half of certain types of aggression such as marital assaults and reported rapes. 11.9% of motor vehicle accidents involve alcohol. A clear and consistent pattern throughout the report showed that the rate of alcohol involvement increases with the amount of damage associated with the problems. If one driver involved in an accident had been drinking it is more likely that someone will be hurt. Even if no one is injured, accidents in which drinking is implicated have higher amounts of property damage than do those in which no one was drinking. Aggressive acts which produce greater physical damage have relatively higher rates of alcohol involvement than do acts which have no alcohol use.

The EFS has been developed to satisfy the critical need for epidemiologic information on drug related problems in Canada. To accomplish this the following are required:

1) sound epidemiologic knowledge base
2) regionalization and decentralization of research
3) suitably trained researchers

The EFS has been designed to satisfy these objectives.

Publications:

1) Drug Related Problems in Hamilton-Wentworth, Report of the Epidemiologic Field Station, Clinical Epidemiology and Biostatistics, McMaster University, Summer, 1976 50 pp.

2) Gerson, L.W., Preston, D., and Golshani, S., "An Epidemiologic Field Station and Non-Medical Drug Use", presented at the Canadian Foundation on Alcohol and Drug Dependence, June, 1976

3) Gerson, L.W., Preston, D., and Golshani, S., "A Surveillance System for Alcohol and Drug Related Problems", presented at the Society for Epidemiologic Research, in Toronto, June, 1976, American Journal of Epidemiology, Vol. 104 #3, Sept. 1976, 345 (Abstract)

4) Chopra, K., Preston, D., and Gerson, L.W., "A Comparison of Employer or Self Referred Workers to an Alcoholic Rehabilitation Program", accepted for presentation at Canadian Foundation on Alcohol and Drug Dependencies, July, 1977

5) Preston, D., "Light and Heavy Drinkers in a Skid Row Service", accepted for presentation at Canadian Foundation on Alcohol and Drug Dependencies, July, 1977

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
H.B.M.Murphy	
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
Groupe Inter-universitaire de Recherche en Anthropologie médicale et Ethnopsychiatrie;Montréal.	
PROJECT TITLE – TITRE DU PROJET	
Pilot testing of a new method of surveying alcohol-abuse and similar disorders.	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES
1976-77	$ 20,750

TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE: 392-5164

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: [ ] EVALUATION – ÉVALUATION [ ] BIOMEDICAL – BIOMÉDICALE [ ] BEHAVIORAL – COMPORTEMENT [x] SOCIAL SCIENCE – SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Project Design

A new survey method depending neither on self-reports nor on medical services is being tested in a small city. The method calls for informants, drawn at random from the population, to report on a limited range of medical and related disorders in themselves, their households, and a list of acquaintances, alcohol-abuse being included in the disorders covered but receiving no special prominence. The technique permits the informants to keep the names of their acquaintances private and confidential, but provides the researcher with basic demographic data on each one having one of the listed disorders.

It is hypothesised that (a) informants will be freer in reporting on alcohol-abuse in acquaintances than in their own households;

(b) the cost of the survey will be considerably reduced, at no loss of accuracy regarding the prevalence of certain types of alcohol-abuse in the population;

(c) the method of enquiring regarding the nature of the alcohol-abuse will permit a differentiation of categories of problem and hence an indication of the categories most requiring attention;

(d) the prevalence of current problems associated with alcohol revealed by this method will be higher than by self-report surveys.

Problems associated with the method, and intended to be explored in part during the research are: (a) alcohol-abusers and non-abusers may not have an equal chance of being included in informants' lists;

(b) some abusers may be named by more than more than one informer;

(c) the information on each case will be quite limited.

It is intended to cover 400-600 informants, each yielding information on 15-20 members of the population. The design of the study will permit a comparison between

(a) male and female informants;

(b) trained and untrained, medical and non-medical interviewers;

(c) prevalence of alcohol-abuse assessed by this method with prevalence assessed through official sources;

(d) prevalence of alcohol-abuse reported in self-reports with prevalence as reported among acquintances;

(e) prevalence of another disorder as reported by this method with prevalence as yielded by (probably fairly accurate) official sources;

(f) results obtained by chosing specific community informants as compared with results obtained by allowing interviewers to select anyone within given row of houses.

Progress.

Field interviews are proceeding according to plan, with good collaboration from public. Substudies to assess whom informants tend to include in their lists of acquaintances, and whether alcohol-abusers in the early stages of their disorder tend to have larger or smaller circles of acquaintances than average, are being undertaken.

Findings.

Nil as yet.

Publications.

Nil as yet.

Relevance.

If validated, the method could reduce the cost of conducting alcohol-abuse surveys, improve the degree to which such surveys reveal alcohol-associated behavior which is socially disapproved, and provide a quicker means of assessing whether changes in alcohol-availability are reflected in changes in alcohol-associated problems.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Kai Pernanen K. Pernanen	Social Studies Dept.
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
Addiction Research Foundation, 33 Russell St., Toronto, Ontario M5S 2S1	
PROJECT TITLE – TITRE DU PROJET	
"Alcohol and Violence: A Pilot Project"	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES
7 months	$17,403

TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE: (416)595-6164

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [ ] BIOMEDICAL BIOMÉDICALE [ ] BEHAVIORAL COMPORTEMENT [X] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The pilot project entitled "Alcohol and Violence" consists of the development of methodology and practical arrangements for the proposed study: "Alcohol and Aggressive Behaviour: A Community Study with a Crosscultural Perspective" (RODA Application 1212-5-236). Three different data collection techniques will be used in the actual study:1) An interview study of 1200 Thunder Bay residents, 2) An observational study in a sample of Thunder Bay drinking establishments, and 3) A one-year study of police reports on violent crimes incoming to the Thunder Bay Police Force, running concurrently with the interview and observational studies. A crosscultural aspect of the study will include 1) a replication of the study in a community in Finland to be funded locally, and 2) an oversampling of Thunder Bay residents of Finnish origin to be included in the interview study. The preparation of the interview study have included: selection of a sampling frame, development and pretesting of interview schedule, and revision of the interview schedule on the basis of an analysis of pretest results. For the study of police records on violent crime, a coding schedule has been developed in consultation with the Thunder Bay Police Force. Information on the extent of alcohol involvement of offender and victim will be collected for each case. The methods and data collection instruments for the observational study have been pretested in a small sample of Toronto taverns.

During a visit in Thunder Bay contacts were made with relevant individuals and organizations in the community to secure local knowledge and support of the project. With reference to the crosscultural aspect of the study, cooperation has been established with the Finnish Foundation for Alcohol Studies for a replication in a community in Finland.

The findings at this stage pertain to the feasibility of an intensive community study on the relationship between alcohol use and aggressive behaviour in the proposed location. This feasibility has been well confirmed. Cooperation from the local police force has been established as well as practical arrangements with the Addiction Research Foundation's Regional

Office etc. To this point the pretests have established the feasibility of collecting data on personal experiences of aggressive behaviour and attitudes towards drinking, drunkenness and aggression by using an interview survey method. Also, the feasibility of collecting observational data on patterns of interaction and emotional behaviour in tavern settings has been established, as has the instrument for coding information from incoming police reports on violent crime. The significance of the results of the pilot project is to a large extent dependent on the realization and execution of the proposed main study. The main project addresses itself directly to the major problem area of alcohol use and aggressive behaviour. It will study the strength of the association and specify the alcohol use patterns, settings, personal characteristics, attitudes etc. which influence the relationship. A causal accounting of the relationship will be attempted by interpretations of the correlational data and an analysis of interactional patterns in connection with alcohol use. The specification of causal factors and the arrival at estimates of the incidence of aggressive behaviour in connection with alcohol use both have important implications for both social policy and basic research.

The data collection on police reports of violent crime has started as of April 1, 1977 and will continue until March 31, 1978. The collection of observational data on behaviour in drinking establishments in Thunder Bay is scheduled to begin in the middle of May 1977. The main part of the observations and the interview study will be carried out in September-November of 1977.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Schlegel, R. P. R. Schlegel	Kinesiology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Waterloo, Waterloo, Ontario.

PROJECT TITLE – TITRE DU PROJET
A Social Psychological Study of Non-Medical Drug Use in Secondary School and College Students

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-77	$92,745.	885-1211, ext. 3089

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[ ] BIOMEDICAL – BIOMÉDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[XX] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

The research aims principally to study the relationship of attitudinal, social expectancy, perceived social environment, personality and selected demographic variables to marijuana smoking and the use of tobacco, alcohol, amphetamines, barbiturates, heroin, hallucinogens, solvents, and tranquilizers. A longitudinal survey design included 5 data points with the first 4 being 4 months apart and the fifth being held 12 months after the fourth test session. This testing schedule will permit sufficiently small time units to capture the more subtle psychological changes as well as a two-year time span to enable study of longer term trends in consumption levels and patterns of drug use. The order of psychological change versus behaviour change is presently being examined during this two-year period. Also, classes of drug use and attitudes toward these drugs are being investigated with special attention to those "pathways" which lead to alcohol use and its increased consumption. Two secondary school systems (one urban in orientation, the other more rural and small town) provided a total sample of approximately 2,000 students for participation in the research. Also, some experimental research has been conducted to assess the effects of persuasive communications on drug attitudes and behaviour. Finally, the relationship of internal-external locus of control to drug use is being examined with a college population.

Various analyses are presently in progress. Papers resulting from this research which are in press or submitted include:

1. Correspondence and mediational properties of the Fishbein model: An application to adolescent alcohol use. This study indicated the efficacy of the Fishbein model in predicting alcohol use. Findings also suggested that the model's two components (attitudes and normative beliefs) were essentially sufficient predictors when an additional set of 33 variables derived from social learning theory was considered.

2. Proximal cognitive factors differentiating controlled and uncontrolled adolescent alcohol use. Controlled vs. uncontrolled beer drinkers and liquor drinkers respectively were compared on personal beliefs, perceived normative beliefs and probability estimates pertaining to drinking intentions (i.e., cognitive factors which are "proximal" or directed towards the target object, drinking alcohol). Results indicated that controlled and uncontrolled drinkers differed significantly on these proximal cognitive factors. In terms of social context, measures pertaining to party and pub situation discriminated the two drinker types best.

3. Religiosity and adolescent alcohol use. Proscriptive Protestants, Prescriptive Protestants, Catholics and non-affiliates were compared on a quantity-frequency index of alcohol use. Results indicated Prescriptive Protestants and Catholics to have

the highest prevalence of use. However, when only regular users were considered, non-affiliates were shown to have the highest abuse rates. In all cases, Proscriptive Protestants had the lowest rates. Further analyses are continuing to discern mediating variables, especially certain dimensions as derived from a factor analysis of Jessor's religiosity scale.

4. Multidimensionality of internal-external locus of control: Some additional data bearing on the validity of self-control as a third dimension. Three subdimensions of fate, social systems control, and self-control were differentiated by factor analysis thereby replicating Reid and Ware's work. Self-control, however, does not appear to come from a common generalized control orientation domain.

5. Multidimensional locus of control and drug use. Results indicated that the various dimensions of I-E control are differentially related to drug use. Greater externality on self-control was found to be related to the use of depressant drugs. Internals viz. self-control were less likely to avoid the use of excitant drugs. Externality, on fatalism, by contrast, was positively related to all drugs whether depressant or excitant. Social systems control was unrelated to any form of drug use.

6. The role of persuasive communications in drug dissuasion. Preliminary results from an experimental study involving a structured communications approach to changing marijuana attitudes and smoking intentions indicated the complexity of the underlying processes. Some general principles were discussed centred around the question "Who says what to whom with what effect?"

7. A comparison of predictive models for the explanation of varied drug use criteria in different populations. Three different models are being compared in the prediction of varying drug use criteria. The differential predictive utility of these models is explained on the basis of the differential complexity of the attitude structures and behavioural repertoires concomitant with the various criteria.

The significance of the above research and ongoing analyses lies first in the area of problem definition (e.g., extent of alcohol abuse) and secondly with respect to explaining various patterns and progressions of drug use. Different sets of explanations will be available as a basis for developing programs of primary and secondary prevention as well as for treatment. Problems will only be reduced in the long term as programs are firmly based on such scientifically-derived principles. Future research will be directed at those variables in our explanatory models which are amenable to change.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. E.M. Sellers	Intensive Care Unit & Clinical Pharmacology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Clinical Institute, ADRF, 33 Russell Street, Toronto, Ontario. M5F 2F1

PROJECT TITLE – TITRE DU PROJET
A STUDY OF EPIDEMIOLOGY, TREATMENT AND ANALYTICAL SERVICES IN ADULT ACUTE DRUG INGESTION

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-1977	$74,450.00	368-2581

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[ ] BIOMEDICAL – BIOMÉDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[X] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

DRUG ANALYSIS IN MANAGEMENT OF DRUG OVERDOSE

Detailed surveillance of drug overdose patients presenting to the emergency departments of 21 acute care Toronto hospitals is being carried out to determine: 1) patient characteristics; 2) regional variations in overdosage patterns; 3) variations in acute management; and 4) the usefulness of quantitative and qualitative drug analysis in clinical management. A majority of overdose patients (approx. 70%) in all hospitals had toxicologic drug analysis ordered by the treating physician. Blood, urine and gastric drug analysis constituted 73%, 24% and 26% respectively of 7958 requests (6 months). Yield on serum analysis is low and this pattern of sample submission is inefficient. Only 25% of samples analyzed were positive for any drug and only 10% contain all drugs allegedly taken. Patient history is unreliable. In 190 patients allegedly ingesting only ethanol, barbiturates 24%, salicylates 9%, nonbarbiturate sedatives 8%, bromides 5%, nonsalicylate analgesics 4%, phenothiazines 4%, antidepressants 3%, solvents 3%, narcotics 1% were found. Despite the inaccuracy of history there is no evidence to date that costly toxicologic analysis is efficiently requested or that it contributes significantly to decrease morbidity and mortality in overdose patients.

ADVERSE REACTIONS DUE TO ANTIMICROBIAL DRUGS

Adverse drug reactions must be evaluated by balancing severity and frequency vs clinical indications and therapeutic potential. Data have been collected prospectively on 1,600 hospitalized patients receiving ampicillin, gentamicin, or any cephalosporin. In the first 817 patients, 23% had proved infection; 12% received chemoprophylaxis, and 65% received sympotamtic therapy. Prior to antimicrobial therapy, only 70% of patients had specific investigation other than a white blood cell count (WBC) and 48% were febrile. A differential WBC was performed in only 329 patients (40%). Gram staining was done in 15% of cases. Of 215 patients who received therapy for pulmonary infection (prophlaxis excluded), 94 had an investigative chest x-ray and 36 had a sputum Gram stain. Infectious diseases are clearly assessed incompletely, and antimicrobials are often used without an adequate data base. While antimicrobials may be overused, it is impossible without complete investigation to define an acceptable occurence rate for adverse reactions to ampicillin, gentamicin, or cephalosporins.

...2

PREDICTABILITY OF EMERGENCY DRUG ANALYSIS

In a prospective study on the epidemiology and management of adult drug ingestion and abuse, the accuracy of reporting by patients was investigated. The levels of consciousness were also compared with drug levels.

3548 patients were seen during Jan-June 1975 in the emergency rooms of 21 hospitals in Metropolitan Toronto, Bromides 100%, Barbiturates 83%, Salicylates 81%, Ethanol 78%, Tricyclic antidepressants 63%, non-Barbiturate sedative-hypnotics 59%, Phenothiazines 48% and Benzodiazepines 46% were found in patients in whom these drugs were alleged and tested for. The incidence of drugs in patients who did not allege them were, Barbiturates 26%, Salicylates 24%, Bromides 21% and Benzodiazepines 21%. Drug analysis was done using GC and TLC.

Lower limits of detections using GC were such that "therapeutic" amounts could be detected. Lower limits of detection for Diazepam and Chlordiazepoxide were 1.25 and 2 mg/l. Low detection percentage for Benzodiazepines in both alleged and non-alleged groups could be due to methodology.

In 531 patients, only a single drug was identified. No correlation was found in these patients between their drug levels and level of consciousness. There is a great scatter e.g. with diazepam <2 mg/l 50 were alert, 45 drowsy, 15 unconscious; with amobarbital+secobarbital (Tuinal) <12 mg/l 5 were alert, 7 drowsy, 4 unconscious; with ethanol <800 mg/l 26 were alert, 14 drowsy, and 5 unconscious. This is not surprising as many factors (disease status, drug habits etc.) influence the drug level.

As there is a high rate of correct identification in reporting and a poor correlation in drug levels, the value of quantitative emergency drug analysis is questionable.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
R Hoon	PSYCHOLOGY DEPARTMENT

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

University of British Columbia, Vancouver, B.C. V6T 1W5.

PROJECT TITLE – TITRE DU PROJET

Observational Study of Alcohol Consumption in Natural Settings.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1975-76	$41000	228-3008

FIELD OF RESEARCH SUJET DE LA RECHERCHE

- ☐ EVALUATION ÉVALUATION
- ☐ BIOMEDICAL BIOMEDICALE
- ☐ BEHAVIORAL COMPORTEMENT
- ☑ SOCIAL SCIENCE SCIENCES SOCIALES
- ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The purpose of this study was to obtain quantitative descriptive data on drinking behaviour in public drinking establishments, in particular to estimate the amount of alcohol consumed at a single sitting, the rate of consumption, and the correlates of these variables.

Two three-man teams of observers were stationed in four beer parlors and four cocktail lounges in Vancouver, on eight successive week-ends. Observations were made on two nights, Friday and Saturday, in each of these locations, from 7 p.m. to closing. Each team selected a number of tables and unobtrusively recorded sex, estimated age and weight, number in party, duration of the occasion, number and type of drink per subject, and the time interval of each successive drink. The total sample of subjects observed was about 600 in beer parlors and 800 in cocktail lounges. These data were obtained from October through December, 1975.

A second, smaller sample was observed from January through March, 1976, using the same procedures, but recording times of individual sips in order to make it possible to explore in more detail drinking rates and styles and their correlates.

In order to obtain in a preliminary way some notion of the amount of drinking by patrons prior to and subsequent to a particular visit to a drinking establishment, patrons were approached on their departure and invited to phone an interviewer some evening of the following week. The rate of completed interviews were approximately 20% of those approached and the total number of interviews is about 200. The interview schedule was brief, but included information on distance travelled, mode of transportation, prior and subsequent drinking, nature of the occasion, subjective intoxication, and basic demographic information.

Simple tabulations of the basic variables were tabulated for each drinking location, with a primary emphasis on the comparison of beer parlor and cocktail lounge. The beer parlor, relative to the cocktail lounge is a male preserve: 72% of the beer parlor sample were male; 55% in the lounge. Beer parlor patrons stayed on an average of an hour and a half, cocktail lounge patrons about an hour. Beer parlor patrons drank about four beers, lounge patrons about two drinks. The modal group size in both types of establishment was two, but the distributions were very different - solitary drinkers were much more common in beer parlors and were exclusively male in both types of location; they drink one drink fast, and leave, typically. The distribution of group sizes is a familiar, positively skewed curve in beer parlors - although the mode is two, 66% are in groups larger than two, and one-third in groups of five or more. The distribution of group sizes in cocktail lounges is bimodal, 80% of patrons being in groups of two or four. Lounge patronage tends strongly to be in couples, an interpretation which is borne out by the sex composition of the groups.

Relationships between variables tended to confirm findings in an earlier study in the beer parlor. Number of drinks was strongly related to duration of the occasion, which in turn was moderately related to the group size. These relationships are much weaker in the cocktail lounge. There was no consistent relation between drinking rate and group

continued page 2....

size except for the much shorter time per drink by solitary male drinkers. There was a marked sex difference in drinking rate in beer parlors, the average interval for women being 5 to 10 minutes greater than for men. This difference was greatly reduced in lounges, largely because of a decrease in the rate of men's drinking. For both sexes, the time per drink is greater in the lounges. The general picture is one of more leisurely drinking, in smaller groups, for shorter periods in the cocktail lounge than in the beer parlor.

We estimated B.A.C. at the time of departure from the establishment. Subject to the errors involved in our various estimates, apprxoimately 30% of beer parlor patrons and 16% of cocktail lounge patrons left with B.A.C. above .08. The interview sample is unrepresentative of the observed sample in that they drank more within the sampled establishment (an average of 5 drinks). A substantial proportion of those interviewed reported drinking before arriving at the establishment where they were contacted, and many drank somewhere else before returning home. All but a very few were driving or were passengers in private vehicles. There seemed to be no tendency in our small sample for the more impaired to be less likely to drive. The interview data suggest the probability that the observational data underestimates, possibly by a substantial amount, the total alcohol consumed by patrons during the evening.

APPENDIX

Names of all Principal Investigators and their project titles

APPENDICE

Nom des chercheurs principaux et les titres de leurs projets

NOVA SCOTIA
NOUVELLE-ÉCOSSE

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
ECOBICHON, D.J.	The Placental and Milk Transfer of Chronic Low Doses of Methadone, its Pharmacokinetics and Effects on Morphological and Biochemical Aspects of Hepatic Function in the Neonatal Guinea Pig
GAMBERG, H.	The Process of Ideological Change in Corrections: Some Nova Scotian Cases
RUOTOLO, R.	The Atlantic Region Research and Development Team for Drug Treatment Programs

QUEBEC
QUÉBEC

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
AMIT, Z.	Hypothalmic and Limbic Mechanisms of Drug Intake and Dependence
BELLEAU, B.	In Vivo-N-Dealkylation of Opiates in Relation to Agonist-Antagonist Actions
BIRMINGHAM, M.K.	Effects of Delta 9 (Δ^9) Tetrahydrocannabinol on Mitochondriaz Respiration
CAILLÉ, G.	Détermination de la phencyclidine plasmatique et urinaire chez le chien corrélation avec l'activité de la créatine phosphokinase sérique
HOSEIN, E.A.	A Subcellular Model from Brain Which Likely Reflects Changes Taking Place in the CNS of Rats Subsequent to Administration of Opiates and their Antagonists
JOLY, J.G.	Alcoolisme et biotransformation microsomiale hépatique
MERGLER-RACINE, D.	Les effets combinés d'alcool, d'un antihistaminique et du bruit intravéhiculaire sur la performance des conducteurs d'auto
MILSTEIN, S.L.	Traitement de l'abus des drogues: recherche et développement
MURPHY, H.B.	Pilot Testing of a New Method of Surveying Alcohol Abuse and Similar Disorders

QUEBEC
QUÉBEC

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
NOSAL, G.	Consequence of Maternal Narcotic Dependence on Infant Animal Experimental Studies Involving Short-term Effects
NOWLIS, D.P.	Training in Voluntary Self-Governance of Patients with Self-Governance Disorders: Effects on Non-Medical Drug Abuse
PIHL, R.O.	Extra Pharmacological Factors in Drug Intoxication
RANGNO, R.E.	Non-Medical Use of Drugs in Suicide Overdose Research into some Problems
WISE, R.A.	Neural Mechanisms of Brain Self-Stimulation and Amphetamine Self-Administration

ONTARIO

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
BASRUR, P.K.	Studies Related to the Test Systems and Biological Activities of Cigarette Smoke
BROWN, I.R.	Effect of Psychotropic Substances on Gene Activity in Neural Tissue
FORBES, W.F.	The Waterloo Smoking and Health Project
GENT, M.	Establishment of a Pilot Epidemiologic Field Station of Drug-Related Problems
GILBERT, R.M.	Temporal and Volitional Factors in the Development and Assessment of Physical Dependence on Ethanol in Rats
GOLDSTEIN, S.	Cultured Human Fibroblasts: An In Vitro System to Detect Toxic Effects of Delta 9 THC
HIRST, M.	Studies into Behavioural, Neurochemical and Treatment Aspects of Heroin and Ethanol Intoxication
HSIA, J.C.	Application of Stable-Isotope Labelling to the Prevention of Drug Abuse Compliance in Methadone Programs
HUNDLEBY, J.D.	Individual and Environmental Predictors and Correlates of Adolescent Drug-Related Behaviour
JONEJA, M.G.	Teratogenic and Cytogenic Effects of Delta 9 Tetrahydrocannabinol in Rodents
KALOW, W.	Cocaine Disposition and Tolerance

ONTARIO

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
KOHN, P.	Personality Social and Functional Determinants of Youthful Drug Use Patterns
LAVERTY, S.G.	A Proposal for the Study of Non-Medical Drug Use Treatment in Frontenac County
MACCONAILL, M.	Mechanisms of Adverse Reactions to Psychotropic Drugs
MACLEAN, A.	Performance During Sleep: A Paradigm of Drug Evaluation
MAYERSOHN, M.	The Disposition and Response Kinetics of Disulfiram in Dogs
MAZURKIEWICZ-KWILECKI, I.M.	Pharmacological Studies of Mandrax and Methaqualone
PAPPAS, B.	An Exploratory Investigation of Pavlovian Mechanisms in Morphine Tolerance
PEACHEY, J.E.	A Study of the Citrated Calcium Cabimide-Ethanol Interaction with Implications for its Use in an Innovative Controlled Drinking Program for Alcoholics
PERNANEN, K.	Alcohol and Violence: A Pilot Project
SADAVA, S.	A Longitudinal Social Learning Study of Non-Medical Drug Use in Adult Working Samples

ONTARIO

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
SCHLEGEL, R.	The Effects of Factual Value-Oriented and Decision-Making Alternative Exposures on Alcohol Attitudes and Behaviour Under Changing Social Situations: Evaluation of an Educational Program
	The Prediction and Inoculation of Marijuana Smoking Behaviour in Secondary School Students
SELLERS, E.M.	A Study of Epidemiology, Treatment and Analytical Services in Adult Acute Drug Ingestion
SIMPSON, H.M.	Alcohol and Drug Involvement in Traffic Accidents and Fatalities
SMITH, J.A.	Synthesis of Radiolabelled Tetrahydrocannabinol Derivatives
STRETCH, R.	Experimental Investigations of Behavioural and Pharmacological Determinants of Drug-Dependency in Monkeys
TONG, J.E.	Effects of Ethanol and Tobacco on Human Performance and Physiological Variables
VOGEL-SPROTT, M.	The Relation of Drinking Habits and Self-Evaluation of Drugged Performance to Blood Alcohol Discrimination
ZAMEL, N.	Reversability of Pulmonary Function Abnormalities in Cigarette Smokers after Cessation of Smoking

MANITOBA

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
HAVLICEK, V.	Abnormalities of Brain Electrical Maturation of Sleep States in Newborn Infants of Chronic Alcohol Mothers
LANGE, D.E.	Regional Research Team
REID, A.E.	A Study of the Organization of Alcohol and Drug Treatment Centres in Manitoba
WILSON, A.J.	Disulfiram Implantation in Chronic Alcoholics

SASKATCHEWAN

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
HETHERINGTON, R.	Teenage Alcohol Consumption: An Epidemiological Baseline in Saskatchewan Schools
HINDMARSH, K.W.	Development of Rapid Forensic Procedure for the Analysis of Selected Drugs
PIPER, G.	Evaluation of Early School Education in Smoking and Health

ALBERTA

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
ADAM, F.C.	New Methods in Immunoassays Using Florescent Labels
CLARK, S.	Clinical Assessment of Opiate-Like Drugs and Their Antagonists in Man
ZELHART, P.F.	Research On Treatment Program Development: Phase I

BRITISH COLUMBIA
COLOMBIE-BRITANNIQUE

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
ABBOTT, F.S.	Study of the Metabolism and Pharmacolinetics of Methadone and Acetylmethadol: Drug Interactions, Novel Metabolites and Methods for their Detection and Analysis
BEST, J.A.	Smoking Withdrawal Procedures Tailored to Individual Reasons for Smoking
CAMPBELL, D.J.	Hospital Based Reference Drug Abuse Analytical Laboratory, Lower Mainland, B.C.
CUTLER, R.E.	Alternatives Program for Alcohol and Drug Dependency
DAVIDSON, P.	Drug and Alcohol Treatment Programme Development British Columbia and Yukon
FIBIGER, H.C.	Neurochemical Substrates of Drug-Reinforced Behaviour
MCGEER, E.G.	Effects of Methadone on Male Sexual Function and Viability of Progeny
MCGEER, P.L.	Possible Structural and Biochemical Alternatives in the Brain Tissue Following Delta-9-THC Administration
PINEL, J.P.	The Effects of Repeated Withdrawal on the Severity of Abstinence Convulsions
STORM, T.	An Observational Study of Alcohol in Natural Settings